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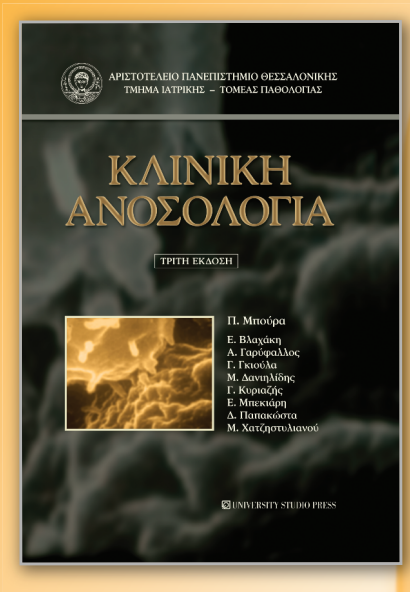

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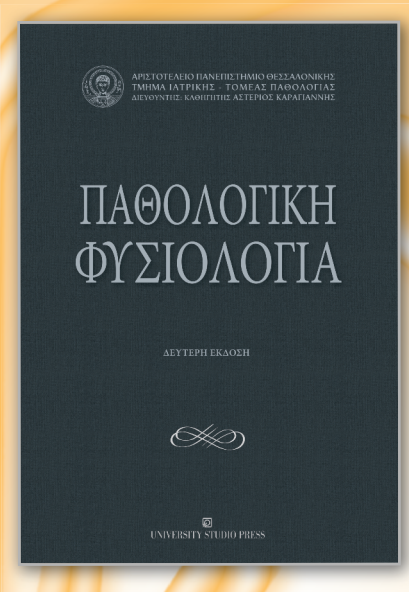

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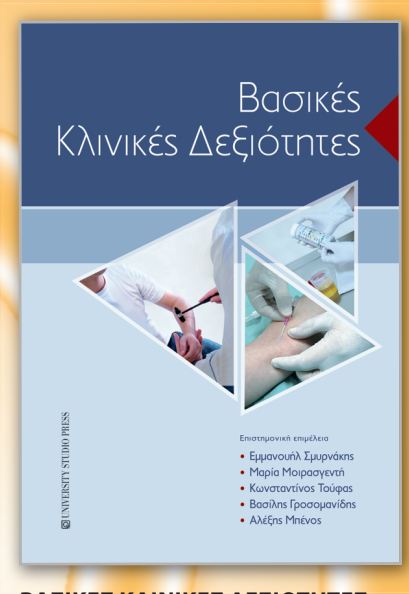

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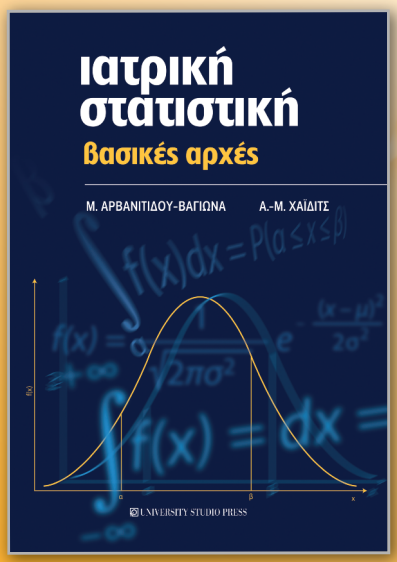

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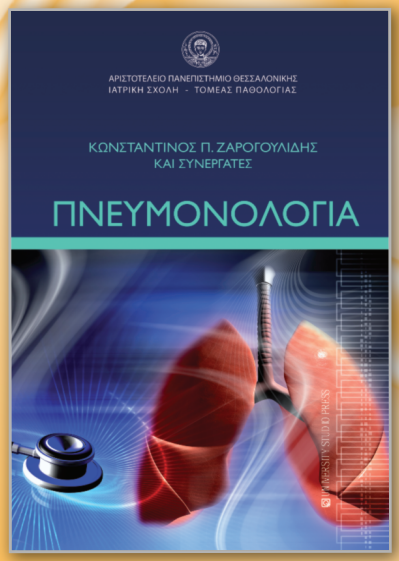

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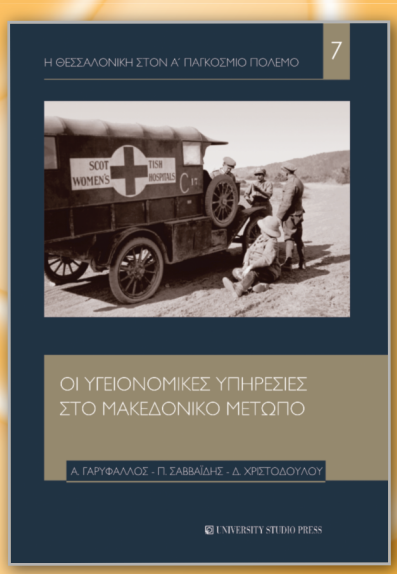

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Review

Diagnostic value and clinical relevance of anti-ribosomal P antibodies in a cohort of Greek SLE patients

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ABSTRACT

Antibodies against ribosomal constituents, present in the serum of SLE patients, were shown to react with the three specific phosho-proteins, P0, PI and P2, of the large ribosome's subunit. Today, these autoantibodies are detected in routine laboratory practice, by less (IIF) or more sensitive methods (immunoblot and ELISA). Clinical studies on their clinical and serological associations have proposed neuropsychiatric SLE (NPSLE), nephritis and hepatic involvement as common complications in seropositive anti ribosomal P antibodies, while a strong relationship with anti-cardiolipin antibodies has been reported. However, until today, a clear and uniform consensus among different groups has not been reached. Thus, this study aimed to provide more insight into these obscure associations. Studying retrospectively a cohort of 131 consecutive SLE patients and 140 patients with other rheumatic diseases we concluded that the presence of anti-ribosomal P antibodies define a subgroup of SLE patients with earlier disease onset and neuropsychiatric manifestations. It is suggested that SLE patients, especially those of young ages, to be tested for anti-ribosomal P antibodies by sensitive methods, since their high association with NPSLE could be a valuable parameter to disease management.

Key words: anti-ribosomal P antibodies, Systemic Lupus Erythematosus (SLE), Neuropsychiatric SLE (NPSLE), diagnostic assays.

Introduction

Twenty years after the first description, in 1965, of anti-ribosomal P antibodies (anti-ribo P abs) as an immunological reactivity against unknown ribosomal constituents, present almost exclusively in Systemic Lupus Erythematous (SLE) patients serum[1], Elkon's studies revealed that the major antigenic determinant for these autoantibodies is a 22-mer peptide, present in the carboxyl-terminus of P0, PI and P2 ribosomal phospho-proteins[2,3]. Subsequently, a strong association between these autoantibodies and Lupus Psychosis was proposed[4].

Importantly, these findings paved the way for research on the clinical significance of anti-ribo P abs in Autoimmune Connective Tissue Diseases (ACTD). A picture soon emerged that their presence represents a highly specific serological marker for SLE, even in the absence of other autoantibodies. However, their clinical and serological associations still remain obscure, since conflicting results have been reported in the literature. Differences in the clinical approach of SLE patients, differences in the diagnostic assays used[5] as well as both genetic and environmental influences[6] may account for these inconsistencies.

More specifically, during the years that the research has been conducted, several changes in the criteria used for the patients' collection have been reported. So in 1997 the American College of Rheumatology (ACR) revised the classification criteria for SLE[7], and also in 1999 established a standardized nomenclature system for the NeuroPsychiatric syndromes of

Systemic Lupus Erythematosus (NPSLE)[8]. Additionally, many different diagnostic platforms with varying sensitivities and specificities can be employed for the serological investigation in SLE, such as Indirect ImmunoFluoresence (IIF), Double ImmunoDiffusion (DID), Enzyme-Linked ImmunoSorbent Assay (ELISA), RadioImmunoAssay (RIA) and ImmunoBlot (IB)[9], while home-made assays are being replaced by more robust and reproducible commercially available kits. Finally, recent genetic studies, point out patients' stratification according to genetic ancestry[10,11].

The aim of the present study was a) to compare two routine laboratory assays, used for anti-ribo P abs detection, b) to determine their diagnostic value for SLE and c) to investigate their possible associations with clinical manifestations and serological findings.

Materials and Methods

SLE patients referring at our tertiary health care center from 2012 to 2014 (in a three years period) were considered for the study. After carefully reviewing their medical files, the cohort included 131 consecutive SLE patients, fulfilling the ACR criteria [11]. The control group consisted of 60 Rheumatoid Arthritis, 60 Sjögren Syndrome, 10 Mixed Connective Tissue Disease and 10 with Systemic Sclerosis, patients. All groups studied were of Greek origin. Patients' data were kept anonymously, under consideration of the Helsinki Declaration of human research ethics, while written consent was not required due to the retrospective study design.

The samples were tested by IIF for the presence of anti-nuclear and anti-ribo P abs (QUANTA Lite™ ANA, Inova Diagnostics, Inc, USA), line IB for the presence of autoantibodies against Sm (B and D), RNP (70, C and A), SS-A (Ro52 and Ro60), SS-B, and ribosomal-P antigens (INNO-LIA™ ANA Update, Innogenetics, Belgium), Farr Assay RIA for the presence of anti-dsDNA autoantibodies (IBL International, GMBH, Germany) and ELISA for the presence of both anti-cardiolipin (Quanta Lite, INOVA Diagnostics Inc., San Diego, USA) and anti-b2GPI autoantibodies (BL Diagnostika, Mainz, Germany). NIKON ECLIPSE E400, Auto-LIA II (Innogenetics, Belgiun), Cobra II Auto Gamma (Canbera Company), DSX System (ThermoLab System, USA) and PR2100 (Sanofi, Pasteur, France) instrumentation was used for each method, respectively. Cut-off values were determined according to manufacturer's protocol. Interpretation and validation of the results were conducted by two well experienced scientists.

Student's t test was performed for continuous variables. For comparison between groups, Fisher's exact test was used. Statistical significance was considered at $p < 0.05$.

Results

The prevalence of anti-ribo P abs among SLE patients was 11.4% (15/131) and 6.1% (8/131), as determined by line IB and IIF respectively. Regarding the control groups, anti-ribo P abs we're not detected by any method. Thus, the sensitivity, specificity, negative predictive value and positive predictive value for SLE diagnosis among ACTD patients, is 11%, 100%, 55% and

Table 1. Demographic characteristics, clinical and serological associations for seropositive and seronegative anti-ribo P abs SLE patients are presented.

	anti-ribosomal P seropositive		anti-ribosomal P seronegative		*p*
	N	(%)	N	(%)	*value*
Patients	15	(11)	116	(89)	-
Men	1	(7)	12	(10)	n.s.
Mean age of disease onset, years ± SD	24 ± 8		39 ± 12		0.000
Arthritis	6	(40)	74	(64)	n.s.
Skin manifestations	7	(47)	82	(71)	n.s.
LN	4	(27)	30	(26)	n.s.
NPSLE	6	(47)	9	(13)	**0.004**
Hepatic manifestations	1	(7)	2	(2)	n.s.
Anti-dsDNA (-)	3	(20)	25	(22)	n.s.
Anti-ENA (-)	4	(27)	43	(37)	n.s.
Anti-PL (-)	4	(27)	14	(12)	n.s.

PL: PhoshoLipid, ENA: Extractable Nuclear Antigens, LN: Lupus Nephritis, NPSLE: NeuroPsychiatric Systemic Lupus Erythematosus

Table 2. Diagnostic properties of anti-ribo P antibodies for NPSLE.

Relative Risk (95%CI)	4.3 (1.8-11)
Odds Ratio (95%CI)	5.9 (1.9-19)
Sensitivity (95%CI)	0.47 (0.21-0.73)
Specificity (95%CI)	0.87 (0.80-0.93)
PPV (95%CI)	0.32 (0.14-0.55)
NPV (95%CI)	0.93 (0.86-0.97)
LR (Likelihood Ratio)	3.6

100% by line IB and 6%, 100%, 53% and 100% by IIF. Since line IB had better diagnostic performance compared to IIF, it was used for the additional analysis.

To investigate possible clinical and serological associations, SLE patients were grouped according to their anti-ribo P seronegative and seropositive status. In table I, demographic characteristics, clinical manifestations and serum markers are presented for each group. Autoantibody profile was not distinguishable between the two groups, while arthritis, skin manifestations, Lupus Nephritis (LN) and hepatic manifestations are presented equally in both groups. On the other hand, patients possessing anti-ribo P abs were characterized by a younger age of disease onset ($p = 0.000$) and NPSLE manifestations (seizures, severe headache, migraine, depression and peripheral neuropathy) were more prevalent in this group ($p < 0.004$).

The results for the diagnostic properties of anti-ribosomal P autoantibodies for NPSLE are shown in table 2.

Discussion

In the present study, the specificity of anti-ribo P abs for SLE differential diagnosis from other ACTD, as detected by IIF and line IB, reaches 100%. The high specificity we found for anti-ribosomal P autoantibodies in SLE is in line with a recent international multicenter evaluation study, reporting 0.7% of 1,113 control patients being seropositive by ELISA[12].

Regarding the sensitivity of anti-ribo P abs in our SLE cohort, this varied depending on the detection method. By IIF (Hep-2 cell substrate), 6.1% of SLE patients possess anti-ribosomal P autoantibodies (figure I), while by line IB this percentage reaches the 11.4% (figure II). The limited sensitivity of IIF for detecting anti-ribo P abs is well known in the literature[13,14]. However, we want to highlight that in a routine clinical laboratory setting, IIF on Hep-2 substrate as a screening tool for

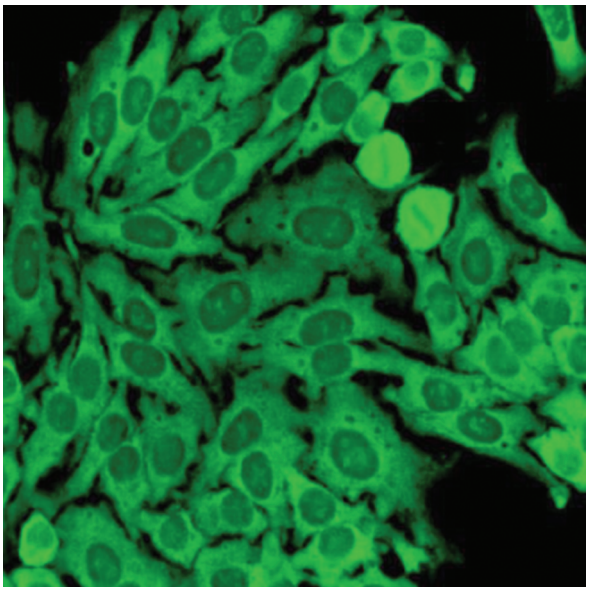

Figure I. *Cytoplasmic Hep-2 staining pattern of anti-ribo P antibodies.*

ACTD assessment is still indispensable and cannot be replaced by any other methods. Positive cytoplasmic staining, compatible with ribosomal pattern, during Hep-2 IIF screening, should always been reported and the

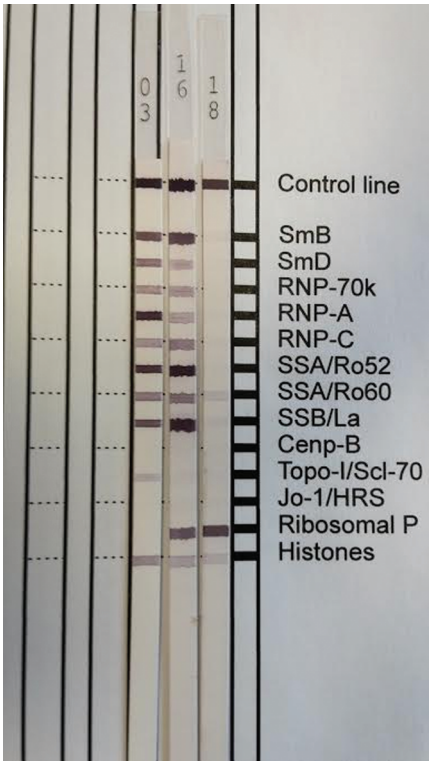

Figure II. *Line staining pattern (immunoblot) of anti-ribo P abs (strip 16 and 18: positive, strip 03: negative).*

patient should be immediately investigated for SLE. Notably, there is a great inter-manufacturer difference in ribosomal pattern on Hep-2 cells[13], and therefore laboratories should always evaluate and be aware of the relative performance of the kit used.

Although several studies show that anti-ribo P abs are strongly clustered with IgG anti-cardiolipin antibodies[15-18], in our SLE patients the proportion of anti-cardiolipin autoantibodies did not differ significantly between seropositive and seronegative anti-ribosomal P patients. The lower reported prevalence of anti-cardiolipin autoantibodies in our SLE patients could have merit as a partial explanation, since it certainly argues for fundamental differences between the studied populations. In line with our findings, Tzioufas *et al.* report a lack of association between anti-ribo P and anti-cardiolipin autoantibodies in an unselected Greek SLE cohort[19].

Regarding clinical associations, our results demonstrate convincingly that the presence of anti-ribo P autoantibodies defines a subgroup of SLE with early disease onset and neuropsychiatric manifestations. Consistently with our findings, a prospective study on 1047 SLE patients suggests anti-ribo P abs as a reliable biomarker for the prediction NPSLE[20]. In addition, according to a recent study that performed a meta-analysis of data on serum and cerebrospinal fluid (CSF) levels and positivity of Abs, NPSLE patients have elevated serum levels of anti-ribo P Abs compared with SLE patients. Furthermore, they suggest that these antibodies could be used as an adjunct diagnostic tool in NPSLE[21]. On the other hand, clinical associations with LN or hepatic manifestations, as has been shown by others[22], were not confirmed in our study. We firmly believe that shedding light on their still obscure associations can be accomplished by more comprehensive, controlled and reliable clinical studies design and this can be achieved by introducing them in the ACR classification for SLE.

Nevertheless, we conclude that anti-ribo P abs are a highly specific marker for SLE, while are strongly associated with NPSLE and younger disease onset. Our suggestions from the laboratory point of view are as follows: a) anti-ribosomal P IIF pattern on Hep-2 substrate, during screening of ACTD patients, should lead to SLE investigation and b) young SLE patients should be tested by more sensitive methods than IIF for anti-ribo P abs, since their presence could predict a neuropsychiatric involvement.

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Ανασκόπηση

Υπολογισμός των αποτελεσμάτων σε (Ραδιο)ανοσολογικές εξετάσεις

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Εισαγωγή

Για να υπολογιστεί η συγκέντρωση μιας προς διερεύνηση ουσίας στον ορό με ισοτοπικές μεθόδους, χρησιμοποιούνται διαφορετικές πρότυπες συγκεντρώσεις της ίδιας ουσίας (**standards**). Αυτές μετρούνται με τις ίδιες συνθήκες που μετρούνται τα προς υπολογισμό δείγματα. Οπως είναι γνωστό, το τελικό αποτέλεσμα των μετρήσεων είναι ενεργότητα, που εκφράζεται σε «κρούσεις» ανά συγκεκριμένο χρόνο μέτρησης (συνήθως ένα λεπτό), δηλαδή **counts per min (cpm)**.

Η **καμπύλη αναφοράς**, λοιπόν, συνιστά τη γραφική παράσταση της κατανομής του σήματος (ενεργότητα στις ραδιομετρικές εξετάσεις) μεταξύ ελεύθερου (free) και δεσμευμένου (bound) ιχνηθέτη, συναρτήσει της συγκέντρωσης των standards.

Α. Κλασσικός υπολογισμός αποτελεσμάτων των ραδιομετρικών εξετάσεων

Ο παραδοσιακός τρόπος υπολογισμού των αποτελεσμάτων ήταν η τοποθέτηση των αποτελεσμάτων των πρότυπων συγκεντρώσεων σε μιλιμετρέ χαρτί σε σύστημα δύο αξόνων, όπου στον άξονα των Χ (τετμημένη) τοποθετούνταν η συγκέντρωση των standards και στον άξονα των Υ (τεταγμένη) το αντίστοιχο αποτελεσμα σε cpm. Θεωρητικά, εφόσον οι μέθοδοι RIA και IRMA στηρίζονται στον ανταγωνισμό σημασμένου και μη ιχνηθέτη, το αποτέλεσμα θα έπρεπε να είναι μία ευθεία γραμμή (με κατιούσα κλίση στις μεθόδους RIA και με ανιούσα κλίση στις μεθόδους IRMA).

Αυτό που γινόταν στην συνέχεια ήταν η χάραξη οριζόντιας γραμμής που ξεκινούσε από τη θέση των cpm του εκάστοτε άγνωστου δείγματος, η εύρεση του σημείου όπου αυτή έτεμνε την πρότυπη καμπύλη και στη συνέχεια η χάραξη κάθετης γραμμής προς τον άξονα των Χ από το σημείο αυτό. Το σημείο όπου αυτή έτεμνε τον άξονα των Χ, αντιπροσώπευε τη συγκέντρωση του προς μελέτη δείγματος.

Β. Προβλήματα που συνοδεύουν τον παραδοσιακό τρόπο υπολογισμού αποτελεσμάτων των εξετάσεων RIA - IRMA

Δυστυχώς, ενώ αυτό θα έπρεπε να είναι το ιδανικό μοντέλο, στην πράξη δεν ήταν έτσι τα πράγματα. Τα σημεία των πρότυπων συγκεντρώσεων (standards) σχεδόν ποτέ δεν ήταν διατεταγμένα σε ευθεία γραμμή στο καρτεσιανό σύστημα συντεταγμένων, αλλά ήταν διασκορπισμένα συνήθως εκατέρωθεν μίας ευθείας γραμμής και στις ακραίες μετρήσεις η γραμμή γινόταν καμπύλη.

Οι λόγοι είναι πολλοί. Μερικοί από αυτούς είναι:

1. Έλλειψη ακρίβειας στην αναρρόφηση του δείγματος (αυτό αντιμετωπίζεται μερικά με τη χρήση διπλών δειγμάτων και τη χρησιμοποίηση του μέσου όρου αυτών ή την απόρριψη τους αν έχουν διαφορά μεγαλύτερη του 5-10%). Η χρησιμοποίηση αυτοματοποιημένων συστημάτων στην εκτέλεση της διαδικασίας και η μη παρεμβολή του ανθρώπινου παράγοντα εξαλείφει μερικώς το παραπάνω πρόβλημα.

2. Η έστω και σε μικρό βαθμό διαφορετική συγκέντρωση του προσροφηθέντος αντισώματος στα τοιχώματα των σωληναρίων.

3. Η **μη ειδική σύνδεση (non specific binding – NSB)**, δηλαδή η σύνδεση του ιχνηθέτη στο σωληνάριο, σε θέση όπου κανονικά δεν έπρεπε να συνδεθεί.

4. Το ανεπαρκές ξέπλυμα των σωληναρίων από το περιεχόμενο τους πριν από τη μέτρηση.

5. Η διαφορετική χημική συγγένεια του σημασμένου ιχνηθέτη σε σχέση με την προς μέτρηση ουσία.

6. Η μέτρηση κρούσεων από το περιβάλλον (background). Το πρόβλημα αυτό λύνεται μερικώς με τη μέτρηση ενός άδειου σωληναρίου και την αφαίρεση των κρούσεων που προκύπτουν, από τα standards και τα δείγματα.

7. Η μη επίτευξη ισορροπίας στην αντίδραση αντιγόνου – αντισώματος.

8. Το γνωστό από την μικροβιολογία **φαινόμενο προζώνης (high dose hook effect)**, που επηρεάζει την μέτρηση των υψηλών συγκεντρώσεων.

9. Το φαινόμενο **low dose hook effect** που κυρτώνει την καμπύλη στις χαμηλές συγκεντρώσεις και οφείλεται συνήθως σε αλοστερική σύνδεση ή σε κατεστραμμένο ή ληγμένο ιχνηθέτη.

10. Αλλοίωση συνήθως των άκρων της καμπύλης από μη ιδανικές συνθήκες pH ή θερμοκρασίας.

11. Η αποσύνδεση συνδεμένου ιχνηθέτη από τα τοιχώματα των σωληναρίων κατά τη διαδικασία του πλυσίματος.

Γ. Μεθοδολογίες υπέρβασης των προβλημάτων κατά τον υπολογισμό αποτελεσμάτων των εξετάσεων RIA - IRMA

Επειδή λοιπόν, για τους παραπάνω λόγους, η διάταξη των σημείων των πρότυπων δειγμάτων στο καρτεσιανό σύστημα συντεταγμένων δεν είναι ευθεία γραμμή, χρησιμοποιούνταν διάφορες μεθοδολογίες για τον υπολογισμό της συγκέντρωσης των άγνωστων δειγμάτων με βάση τη μετρούμενη ενεργότητά τους (Πίνακας Ι).

Όλες οι παραπάνω χειρόγραφες μέθοδοι περιόριζαν σε σημαντικό βαθμό την πιθανότητα απόκλισης των αποτελεσμάτων, αλλά ήταν σε μεγάλο βαθμό εμπειρικές και – όσο ακριβείς και να ήταν – εισήγαγαν λάθη στον υπολογισμό των αποτελεσμάτων.

Δ. Δημιουργία προφίλ επαναληψιμότητας

Σε σύστημα καρτεσιανών συντεταγμένων, στον άξονα των Χ έχουμε τιμές συγκέντρωσης και στον άξονα των Υ τιμές ενεργότητας. Σχεδιάζεται η καμπύλη αναφοράς με βάση τα standards και τα controls. Σε κάθε τιμή συγκέντρωσης αντιστοιχεί και μία συγκεκριμένη κλίση της καμπύλης:

$$\text{Κλίση} = (Y1\text{-}Y2) / (X1\text{-}X2) = \Delta Y / \Delta X$$

Στο σημείο Ρ της καμπύλης σχεδιάζουμε την εφαπτομένη ΡΤ, την οριζόντια γραμμή ΡΥ και την κάθετη γραμμή ΡΧ. Στη γραμμή ΡΧ, προσδιορίζουμε τμήμα ΡS, ίσο με τη διασπορά στο αποτέλεσμα Υ, όπως υπολογίζεται με τη συνάρτηση αποτελέσματος – σφάλματος μέτρησης. Από το S σχεδιάζουμε οριζόντια γραμμή που τέμνει την εφαπτομένη ΡΤ στο σημείο R. Το διάστημα SR αντιπροσωπεύει την τυπική απόκλιση για τη συγκέντρωση Χ. Υπολογίζεται ο συντελεστής μεταβλητότητας CV% (SD×100/X) και σχεδιάζεται το προφίλ επαναληψιμότητας, το οποίο ουσιαστικά είναι η γραφική παράσταση του CV (ΔX/X) συναρτήσει των αντίστοιχων συγκεντρώσεων.

Πίνακας Ι. Χειρόγραφες μεθοδολογίες υπολογισμού συγκέντρωσης δειγμάτων.

Η σύνδεση των σημείων με ευθείες γραμμές. Το αποτέλεσμα είναι μία τεθλασμένη, με αμβλείες γωνίες, γραμμή. Στην συνέχεια σχεδιάζοντας μία οριζόντια γραμμή από τον άξονα των Υ που ξεκινά από τις κρούσεις του προς μελέτη δείγματος, βρίσκουμε το σημείο που τέμνει τη γραμμή των standards και από το σημείο αυτό τραβώντας μία κάθετη γραμμή προς τον άξονα των Χ βρίσκουμε τη συγκέντρωση της προς υπολογισμό ουσίας στο υπό μελέτη δείγμα. Η μεθοδολογία αυτή είναι γνωστή με τον αγγλικό όρο interpolation. Στην προσπάθεια η γραμμή που σχηματίζει η ένωση των σημείων των standards να είναι κατά το δυνατόν ευθεία, χρησιμοποιούνται ανάλογα με την εξέταση – με βάση την εμπειρία – διαφορετικά γραμμογραφημένα χαρτιά, όπως ημιλογαριθμικό ή λογαριθμικό. Προβλήματα προκύπτουν με τα outliers, την ασυμφωνία διπλών προσδιορισμών και όπου παρατηρείται μεγάλη καμπύλωση των σημείων.

Η σχεδίαση ευθείας γραμμής που με το μάτι διέρχεται κατά το δυνατόν εγγύτερα από τα σημεία των standards. Αυτό γινόταν με το σκεπτικό ότι θεωρητικά θα έπρεπε τα standards να είναι διατεταγμένα σε ευθεία γραμμή, επομένως σχεδιάζοντας μία γραμμή που κατά το δυνατόν προσεγγίζει τα παραπάνω σημεία, ελαχιστοποιούμε τα λάθη που έχουν εισαχθεί κατά την εκτέλεση της δοκιμασίας.

Η σχεδίαση καμπύλης γραμμής που περνά κατά το δυνατόν από τα περισσότερα σημεία των standards χρησιμοποιώντας έναν εύκαμπτο χάρακα Με τον τρόπο αυτό αποδεχόμαστε ότι το πρακτικό αποτέλεσμα μίας δοκιμασίας δεν είναι ευθεία γραμμή, αλλά κυρτώνει τουλάχιστον στα άκρα της και ταυτόχρονα ελαχιστοποιούμε τα λάθη που έχουν εισαχθεί κατά την εκτέλεση της δοκιμασίας.

Επειδή συνήθως το προφίλ επαναληψιμότητας αναφέρεται σε ξεχωριστές μετρήσεις, θα πρέπει η υπολογιζόμενη απόκλιση να αντιστοιχεί σε αυτές και όχι στο μέσο όρο των διπλών δειγμάτων. Επίσης, η συγκέντρωση στον άξονα των X εκφράζεται στις στοιχειώδεις μονάδες μέτρησής της και όχι με λογάριθμο ή άλλο μαθηματικό μετασχηματισμό.

Ε. Τρόποι σχεδίασης πρότυπης καμπύλης με τη βοήθεια ηλεκτρονικών υπολογιστών

Με την επικράτηση της χρήσης των ηλεκτρονικών υπολογιστών, ο υπολογισμός των αποτελεσμάτων έγινε ευκολότερος και περισσότερο ακριβής, καθώς εισήχθησαν μαθηματικές μεθοδολογίες στο σχηματισμό της καμπύλης των standards, οι οποίες περιόριζαν σε μεγάλο βαθμό την πιθανότητα λαθών. Ο υπολογιστής εξάγει μια μαθηματική συνάρτηση για την καμπύλη αναφοράς, που του επιτρέπει να υπολογίζει τη συγκέντρωση της υπό διερεύνηση ουσίας σε ένα δείγμα από το επίπεδο της ενεργότητας του δείγματος, όπως προσδιορίζεται ραδιοανοσολογικά, χωρίς την ανάγκη σχεδίασης της καμπύλης. Βέβαια, το πρόγραμμα προσαρμογής καμπύλης παρουσιάζει μία καμπύλη, ώστε ο χρήστης να έχει μια γραφική παράσταση των δεδομένων. Η χρησιμοποιούμενη μαθηματική συνάρτηση για την προσαρμογή των πρότυπων σημείων θα πρέπει να προσαρμόζει την καμπύλη κατά το δυνατόν πλησιέστερα στις συγκεντρώσεις αυτές, δηλαδή η τιμή του συντελεστή προσαρμογής (R^2) να είναι κοντά στη μονάδα (στους ραδιοανοσοπροσδιορισμούς, ο συντελεστής R^2 εκφράζει το ποσοστό της μεταβλητότητας της ενεργότητας που εξηγείται με βάση τις μεταβολές της συγκέντρωσης). Η διαδικασία της προσαρμογής της καμπύλης μπορεί να εισάγει στα αποτελέσματα κάποιο βαθμό πόλωσης ή προβληματικής επαναληψιμότητας. Οι όποιες μέθοδοι ακολουθούνται δεν εγγυώνται 100% επιτυχή επίλυση του ζητήματος, οσοδήποτε περίπλοκες και αν είναι.

Επίσης, πολλές φορές είναι πρακτικό να εργάζεται κανείς με συναρτήσεις των παραμέτρων των καρτεσιανών συντεταγμένων (π.χ. ο λογάριθμος της συγκέντρωσης σε σχέση με το ποσοστό δεσμευμένης ακτινοβολίας, κοκ).

Δύο είναι οι επικρατούντες τρόποι σχεδίασης της πρότυπης καμπύλης:

- ✓ η μέθοδος interpolation και
- ✓ η εφαρμογή ενός μαθηματικού μοντέλου.

Ε.Ι. Τεχνικές interpolation

Βασική παραδοχή στις μεθόδους αυτές είναι ότι οι τιμές που υπολογίστηκαν από τα standards δεν εμπεριέχουν λάθη ή ότι τα λάθη είναι πολύ μικρά, επομένως για να σχηματίσουμε την πρότυπη καμπύλη πρέπει να τις ενώσουμε μεταξύ τους. Αν αυτό γίνει με χρήση ευθύγραμμων τμημάτων, τότε μιλάμε για linear (γραμμικό) interpolation.

Ο μαθηματικός τρόπος που γίνεται ο υπολογισμός της συγκέντρωσης ενός άγνωστου δείγματος είναι ο εξής:

Αν υποθέσουμε ότι cX είναι η ζητούμενη συγκέντρωση του δείγματος και rX είναι οι κρούσεις που πήραμε από αυτό το δείγμα, r1 και r2 είναι οι κρούσεις των γνωστών standards c1 και c2 των οποίων οι κρούσεις αντιπροσωπεύουν την αμέσως μικρότερη και την αμέσως μεγαλύτερη τιμή από αυτήν των κρούσεων του άγνωστου δείγματος, τότε ισχύει :

$$(cX - c1) / (c2-c1) = (rX-r1) / (r2-r1)$$

Λύνοντας της εξίσωση ως προς cX έχουμε:

$$cX = c1 + \{(rX-r1) / (r2-r1)\} \times (c2-c1)$$

Είναι πολύ εύκολο πλέον για έναν προγραμματιστή Η/Υ να υλοποιήσει ένα μικρό πρόγραμμα που θα εφαρμόζει την παραπάνω εξίσωση στις κρούσεις των άγνωστων δειγμάτων και θα υπολογίζει έτσι τις συγκεντρώσεις τους.

Επίσης, αν εφαρμόσουμε την παραπάνω εξίσωση χρησιμοποιώντας όχι τις άμεσα γειτνειάζουσες συγκεντρώσεις, αλλά πιο απομακρυσμένες, μπορούμε να υπολογίσουμε τις αποκλίσεις (bias) που μπορεί να έχει ο υπολογισμός της άγνωστης συγκέντρωσης. Μπορούμε (μιμούμενοι τον χειρόγραφο τρόπο) να δοκιμάσουμε αν η απόκλιση αυτή μπορεί να ελαττωθεί, χρησιμοποιώντας το λογάριθμο των συγκεντρώσεων και στη συνέχεια να πάρουμε τον αντιλογάριθμο του αποτελέσματος, που θα ισούται με την άγνωστη συγκέντρωση.

Μία καλύτερη προσέγγιση είναι αντί να χρησιμοποιήσουμε ευθεία γραμμή (δηλαδή συνάρτηση πρώτου βαθμού) για να ενώσουμε τα σημεία των standards, να χρησιμοποιήσουμε συναρτήσεις μεγαλύτερου βαθμού (Πίνακας 2). Εμπειρικά φαίνεται ότι η καλύτερη μέθοδος είναι η χρήση πολυωνύμων τρίτου (cubic) βαθμού, δηλαδή της μορφής:

$$\psi = \alpha + \beta x + \gamma x^2 + \delta x^3$$

Η μεθοδολογία αυτή συναντάται στα υπολογιστικά συστήματα των γ-counters με τον όρο «**cubic**

Πίνακας 2. Εξισώσεις διαφόρων μορφών προσεγγιστικών καμπύλων.

ευθεία γραμμή	$Y = a_0 + a_1X$
παραβολή (τετραγωνική καμπύλη)	$Y = a_0 + a_1X + a_2X^2$
κυβική καμπύλη	$Y = a_0 + a_1X + a_2X^2 + a_3X^3$
καμπύλη 4ου βαθμού	$Y = a_0 + a_1X + a_2X^2 + a_3X^3 + a_4X^4$
καμπύλη ν-οστού βαθμού	$Y = a_0 + a_1X + a_2X^2 + \ldots + a_nX^n$
υπερβολή	$1/Y = a_0 + a_1X$
εκθετική καμπύλη	$Y = ab^X$ ή $\log Y = \log a + (\log b)X$
τροποποιημένη εκθετική καμπύλη	$Y = ab^X + g$
γεωμετρική καμπύλη	$Y = aX^b$ ή $\log Y = \log a + b(\log X)$
τροποποιημένη γεωμετρική καμπύλη	$Y = aX^b + g$
καμπύλη του Gompertz	$\log Y = \log p + b^X(\log q)$
λογιστική καμπύλη	$1/Y = ab^X + g$

spline», είναι η απλούστερη μορφή της τεχνικής spline-fitting και επιβάλλει περιορισμούς σύνδεσης στα σημεία συνάντησης των τμημάτων που συνιστούν την καμπύλη. Για να είναι ομαλή στο μάτι (smooth) η παραγόμενη καμπύλη, πρέπει να είναι ομαλή η μετάβαση από το ένα τμήμα της καμπύλης (μεταξύ δύο σημείων) στο άλλο (μεταξύ του δεύτερου από τα πρώτα σημεία και του επόμενου). Για να επιτευχθεί αυτό, πρέπει να πληρούνται οι ακόλουθες δύο συνθήκες:

- η κλίση των δύο καμπύλων στα σημεία συνάντησης να είναι ίδια και
- ο ρυθμός μεταβολής της κλίσης των δύο καμπύλων να είναι ίδιος.

Σε πιο μαθηματική γλώσσα αυτό σημαίνει ότι στο σημείο όπου συναντώνται οι δύο καμπύλες θα πρέπει η πρώτη και η δεύτερη παράγωγός τους να είναι ίδιες.

Πλέον περίπλοκες μορφές της τεχνικής διαθέτουν παραμέτρους «λείανσης» (smoothing) της καμπύλης, ώστε η παραγόμενη γραμμή να είναι περισσότερο ευθεία ή περιορίζουν τον αριθμό των σημείων συνάντησης σε ένα.

Οι παραπάνω συνθήκες είναι σχετικά εύκολο να επιλυθούν με τη βοήθεια Η/Υ. Με τη μέθοδο αυτή – που, παράγοντας μαθηματικά ισοδύναμα καμπύλων γραμμών, εφαρμόζεται σε ευρύ φάσμα ανοσοαντιδράσεων – έχει αποδειχθεί εμπειρικά ότι τα αποτελέσματα είναι σχετικώς ακριβή, παρέχουν κάποια προστασία από τα outliers και την ασυμφωνία μεταξύ διπλών προσδιορισμών, ενώ και οι αποκλίσεις από την πραγματικότητα είναι μικρές (εφόσον πάντα ισχύει η συνθήκη ότι τα standards έχουν δουλευτεί με άριστες συνθήκες). Οι απλούστερες μορφές της τεχνικής χρησιμοποιούν τη μέση τιμή ενεργότητας (με τις συνέπειες που αυτό μπορεί να έχει σε περιπτώσεις outliers). Επίσης, πρέπει να αποφεύγεται η «επέκταση» (extrapolation) της καμπύλης, καθώς οι spline-fitting τεχνικές δεν διαθέτουν εγγενείς βιοχημικούς περιορισμούς για το σχήμα της καμπύλης.

Ε.2. Εφαρμογή μαθηματικών μοντέλων και στατιστικών μεθόδων στον υπολογισμό των αποτελεσμάτων

Η εφαρμογή μαθηματικών μοντέλων παλινδρόμησης στη δημιουργία καμπύλων συγκέντρωσης σε μία δοκιμασία στηρίζεται στην υπόθεση ότι οι πραγματικές συγκεντρώσεις των standards αποκλίνουν συνήθως από την υπολογισθείσα τιμή. Το πλεονέκτημα αυτών των μεθόδων είναι ότι προσαρμόζουν τα μοντέλα στα δεδομένα, διορθώνουν μερικώς τα λάθη, βασίζονται στους υποκείμενους φυσιοκοχημικούς μηχανισμούς των ανοσοαντιδράσεων και συνοδεύονται από υψηλή ποιότητα εφαρμογής στην πράξη, παρότι δεν λαμβάνουν υπόψη όλους τους δυνατούς παράγοντες επίδρασης σε μια ανοσοαντίδραση.

Η απλούστερη και συνηθέστερη προσέγγιση στο πρόβλημα είναι η **μέθοδος των ελαχίστων τετραγώνων**. Στη μέθοδο αυτή θεωρούμε ότι η πρότυπη καμπύλη είναι αυτή για την οποία ισχύει η συνθήκη ότι το άθροισμα των τετραγώνων των κάθετων αποστάσεων των σημείων των standards από αυτήν είναι το ελάχιστο δυνατόν, δηλαδή δίνει το μικρότερο άθροισμα τετραγώνων καταλοίπων (sum of squared residuals). Αυτό δεν σημαίνει ότι κατ' ανάγκη περιγράφει τα δεδομένα με τον πλέον ικανοποιητικό τρόπο και στην πράξη μερικές φορές ανακύπτουν απρόσμενα προβλήματα. Τα κατάλοιπα είναι οι διαφορές ανάμεσα στις παρατηρούμενες και στις προβλεπόμενες τιμές. Όταν η παρατηρούμενη τιμή είναι μεγαλύτερη από την προ-

βλεπόμενη, το κατάλοιπο είναι θετικό, ενώ όταν είναι μικρότερη, το κατάλοιπο είναι αρνητικό.

Στην περίπτωση που η γραμμή που αναζητούμε είναι ευθεία (δηλαδή συνάρτηση της μορφής **y=ax+b**) τότε μιλάμε για **ευθεία ελαχίστων τετραγώνων**. Αν η ζητούμενη συνάρτηση είναι μεγαλύτερου βαθμού, τότε μιλάμε για **μη γραμμική συνάρτηση ελαχίστων τετραγώνων**. Η γενική μορφή της συνάρτησης είναι:

$$\psi = \alpha + \beta x + \gamma x^2 + \delta x^3 + \ldots + \omega x^n$$

Η συνηθέστερα αναζητούμενη συνάρτηση είναι τρίτου βαθμού, δηλαδή της μορφής:

$$y=\alpha x^3+\beta x^2+\gamma x+\delta$$

Αποφεύγονται τα μεγαλύτερου βαθμού πολυώνυμα για την αποφυγή ταλαντώσεων της παραγόμενης καμπύλης. Η επίλυση των παραπάνω ζητημάτων με τους παραδοσιακούς μαθηματικούς τρόπους ήταν αρκετά κοπιώδης και έξω από τις συνήθεις ιατρικές γνώσεις. Με την ευρεία όμως εφαρμογή των Η/Υ και με τη σχεδίαση **προσεγγιστικών αλγόριθμων**, δηλαδή **μεθοδολογιών που με διαρκείς επαναλήψεις (iterations) προσεγγίζουν τις σταθερές της ζητούμενης συνάρτησης έως ότου εκπληρωθεί η ζητούμενη συνθήκη**, η εφαρμογή τους αποτελεί πλέον ρουτίνα.

Η πολυωνυμική παλινδρόμηση είναι ιδιαίτερα ευέλικτο μοντέλο με πολύ ικανοποιητική εφαρμογή σε ευρύ φάσμα συγκεντρώσεων και ενεργοτήτων. Μπορεί επίσης η διαδικασία της παλινδρόμησης να είναι σταθμισμένη (weighted regression): λόγω της μεταβαλλόμενης επαναληψιμότητας στο εύρος της καμπύλης, σταθμίζονται τα μετρούμενα σημεία (το «βάρος αποτίμησης» κάθε σημείου είναι το αντίστροφο της διασποράς), ώστε εκείνα με την καλύτερη επαναληψιμότητα να επηρεάζουν περισσότερο την προσαρμογή της καμπύλης. Και εδώ πρέπει να αποφεύγεται η «επέκταση» (extrapolation) της καμπύλης, καθώς οι τεχνικές πολυωνυμικής παλινδρόμησης δεν διαθέτουν εγγενείς βιοχημικούς περιορισμούς για το σχήμα της καμπύλης. Επίσης, πρέπει να αποκόπτεται το τμήμα της καμπύλης στις υψηλές συγκεντρώσεις, καθώς μπορεί να στρέφεται προς τα πάνω (σε ανταγωνιστικές μεθόδους) ή προς τα κάτω (σε ανοσοραδιομετρικές μεθόδους).

ΣΤ. Μοντέλο τεσσάρων παραμέτρων

Ένα άλλο μη γραμμικό μοντέλο που συχνά χρησιμοποιείται είναι το μοντέλο των τεσσάρων παραμέτρων (**Four Parameter Logistic Model - FPLM**), το οποίο είναι επέκταση του μοντέλου logit-log.

Το **μοντέλο logit-log** είναι μαθηματικός μετασχηματισμός που τείνει να καταστήσει ευθεία την καμπύλη αναφοράς, καθώς μοντελοποιεί μαθηματικά τα κύρια φυσικοχημικά στοιχεία των καταστάσεων που η καμπύλη αντιπροσωπεύει. Η logit-log συνάρτηση μετασχηματίζει μια σιγμοειδή καμπύλη με ένα σημείο συνάντησης (το χαρακτηριστικό σχήμα των καμπύλων σε ανοσοαντιδράσεις) σε ευθεία γραμμή. Σε ανταγωνιστικές μεθόδους σημειώνουμε στον άξονα των X το λογάριθμο της συγκέντρωσης και στον άξονα των Y το logit της ενεργότητας, με διόρθωση για το B_0 (ενεργότητα για standard μηδενικής συγκέντρωσης) και το NSB:

$$\text{logit } Y = \ln (Y/1\text{-}Y), \text{ όπου } Y = (B\text{-NSB}) / (B_0\text{-NSB})$$

Για τον υπολογισμό του NSB μπορεί να χρησιμοποιηθεί η τιμή που δίνει ο κατασκευαστής ή κάποια τιμή που έχει εμπειρικά αποδειχτεί χρήσιμη για την καλή προσαρμογή καμπύλης ή ακόμα και να αγνοηθεί, καθώς στις περισσότερες εξετάσεις έχει πολύ χαμηλή τιμή. Το NSB αντιπροσωπεύει την ενεργότητα για άπειρη συγκέντρωση της ουσίας, οπότε σε διενέργεια IRMA, το μαθηματικό μοντέλο είναι ίδιο, αλλά το NSB αντικαθίσταται από το T (υψηλότερη δυνατή ενεργότητα). Τα δεδομένα που προκύπτουν από την εφαρμογή της μεθόδου υφίστανται προσαρμογή, κατά προτίμηση με πολυωνυμική παλινδρόμηση, καθώς τα σημεία στις δύο άκρες της καμπύλης αποκλίνουν από ευθεία γραμμή (λάθη υπολογισμού B_0 και NSB). Κατά την εφαρμογή γραμμικής παλινδρόμησης για την προσαρμογή ευθείας γραμμής σε logit-log γράφημα, υπολογίζονται η κλίση (slope) και η σταθερά (intercept) της καμπύλης (Πίνακας 3). Αν ο μετασχηματισμός logit-log δεν καταστήσει ευθεία τη γραμμή, εισάγεται πόλωση στα αποτελέσματα της εξέτασης, ιδίως στα άκρα της καμπύλης (Εικόνα 6). Είναι σημαντικό να διασφαλιστεί ότι οι κλινικά σημαντικές τιμές δεν επηρεάζονται από την εφαρμογή του μετασχηματισμού.

Στο **FPLM** το υπολογιστικό πρόγραμμα παρέχει 4 παραμέτρους:

- ✓ κλίση καμπύλης - d
- ✓ σταθερά καμπύλης - c
- ✓ άνω ασύμπτωτη καμπύλης –a+b (αντιπροσωπεύει την αληθή τιμή του B_0)
- ✓ κάτω ασύμπτωτη καμπύλης -a (αντιπροσωπεύει την αληθή τιμή του NSB),

σε αντιδιαστολή με τις πειραματικά ευρισκόμενες τιμές του B_0 και το NSB στη logit-log μέθοδο. Η εξίσωση στο FPLM έχει τη μορφή:

Πίνακας 3. Χρήσιμες έννοιες και παράμετροι των ανοσομεθόδων.

- ✓ Ευαισθησία μεθόδου: η μικρότερη ποσότητα της προς ανίχνευση ουσίας που μπορεί να μετρηθεί με τη συγκεκριμένη μέθοδο, δηλαδή η συγκέντρωση της ουσίας που είναι στατιστικά διαφορετική από το μηδενικό standard
- ✓ Επαναληψιμότητα μεθόδου: ο βαθμός στον οποίο συμπίπτουν δύο ή περισσότερα αποτελέσματα του ίδιου δείγματος, μετρημένα με την συγκεκριμένη μέθοδο. Μπορεί να υπολογιστεί για έναν συγκεκριμένο προσδιορισμό (intra-assay) ή για πολλούς διαφορετικούς προσδιορισμούς (inter-assay). Συνήθως εκφράζεται με την τυπική απόκλιση (standard deviation) των μετρήσεων από την μέση τιμή ή με τον συντελεστή μεταβλητότητας (coefficient of variation)
- ✓ Σταθερά (intercept) καμπύλης: η προβλεπόμενη τιμή που παίρνει το y (ενεργότητα), όταν το x (συγκέντρωση) είναι 0.
- ✓ Κλίση (slope) καμπύλης: μέτρο μεταβολής του y, όταν το x μεταβάλλεται κατά μία μονάδα.
- ✓ Θετική κλίση: όταν οι τιμές της συγκέντρωσης αυξάνονται, συναυξάνονται και οι τιμές ενεργότητας.
- ✓ Αρνητική κλίση: όταν οι τιμές της συγκέντρωσης αυξάνονται, μειώνονται οι τιμές ενεργότητας.
- ✓ Μεγάλη κλίση: η ευθεία είναι απότομη, δηλαδή μικρές μεταβολές της συγκέντρωσης επιφέρουν μεγάλες μεταβολές της ενεργότητας.
- ✓ Μικρή κλίση: οι μεταβολές της ενεργότητας συναρτήσει της συγκέντρωσης είναι πιο σταδιακές.

$$y = a + b\,[\exp(c\text{-}d\ln x) / 1 + \exp(c\text{-}d\ln x)]$$

Τροποποιώντας καθεμία από τις παραμέτρους, μπορούμε να δούμε τις προκύπτουσες μεταβολές στο σχήμα της καμπύλης (προσαρμογές στη βάση μαθηματικών συνθηκών).

Το FPLM είναι από τις πλέον αξιόπιστες και ευέλικτες μεθόδους που έχουν αναπτυχθεί για την προσαρμογή της πρότυπης καμπύλης και συνιστά τη βάση των αλγορίθμων προσαρμογής σε πολλά αυτόματα συστήματα. Με κατάλληλο λογισμικό και εφαρμογή προσεγγιστικών αλγόριθμων επιτυγχάνεται η βέλτιστη προσαρμογή της καμπύλης. Απόκλιση από τις θεωρητικές παραδοχές του FPLM παρατηρείται σε high dose hook effect, ανεπαρκή έκπλυση, απομάκρυνση του προσροφημένου αντιγόνου ή αντισώματος από τη στερεά φάση, μη ειδική σύνδεση του ανιχνευτικού συστήματος στη στερεά φάση και σε χαμηλή αναλογία του ενζύμου υπεροξειδάση προς το υπόστρωμα σε ELISA. Σε κάποιο βαθμό αντιμετωπίζονται, αλλά το FPLM παρουσιάζει δυσκολίες στο χειρισμό ασυμμετριών της καμπύλης. Αυτά υπερβαίνονται είτε με προσεκτική στάθμιση των δεδομένων και παραμέτρων είτε με την εφαρμογή του μοντέλου πέντε παραμέτρων:

$$y = a + b\,[\exp(c\text{-}d\ln x) / 1 + \exp(c\text{-}d\ln x)]^m$$

Όταν m=1, τότε η καμπύλη είναι συμμετρική γύρω από το ED_{50}. Το μοντέλο των πέντε παραμέτρων είναι το πλέον ευέλικτο στις ανοσολογικές μεθόδους, καθώς διατηρεί τις μαθηματικές συνθήκες, προβλέποντας και τις παρατηρούμενες στην πράξη αποκλίσεις από τη συμμετρία. Απαιτεί τη μέτρηση 5 standards.

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Ελληνική Εταιρεία Ανοσολογίας

29 Απριλίου
ΠΑΓΚΟΣΜΙΑ ΗΜΕΡΑ ΑΝΟΣΟΛΟΓΙΑΣ

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Ανοσιακό σύστημα και δημόσια υγεία
5ο Συμπόσιο για Πρωτοπαθείς Ανοσοανεπάρκειες –
Παιδιατρική Ανοσολογία,
21 και 22 Απριλίου 2016,
Μουσείο Κυκλαδικής Τέχνης, Αθήνα
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Παγκόσμια ημέρα Ανοσολογίας - DOI 2016

Ανοσολογία χωρίς σύνορα

Η 29η Απριλίου 2016 πλησιάζει!

Η ημέρα αυτή, κάθε χρόνο, είναι αφιερωμένη στην ευαισθητοποίηση του κοινού σχετικά με τον ρόλο της επιστήμης της Ανοσολογίας στην μάχη εναντίον των λοιμώξεων, της αυτοανοσίας, του καρκίνου. Το θέμα του φετινού εορτασμού είναι η:

Ανοσοθεραπεία

η επιστράτευση όλης της δυναμικής που μπορεί να ασκήσει το ανοσιακό σύστημα, η διαχείριση όλων των δυνατοτήτων του, η ενίσχυση της φυσικής ή επίκτητης ικανότητας του προς ένα σκοπό:

Την ανακούφιση από την ασθένεια, την απομάκρυνση από την νόσο, την ίαση

Ο πρώτος εορτασμός της Ευρωπαϊκής Ημέρας της Ανοσολογίας πραγματοποιήθηκε στις 29 Απριλίου 2005 σε περισσότερες από 30 Ευρωπαϊκές χώρες αρχικά. Σημείωσε και συνεχίζει να σημειώνει μεγάλη επιτυχία! Η καθημερινή πάλη για την υγεία που δίνουν οι ανοσολόγοι προβάλλεται στους Ευρωπαίους πολίτες, γεγονός που πιστεύουμε ότι ενδυναμώνει την έννοια της άμυνας του οργανισμού, τον ρόλο της ανοσολογίας στην κοινή συνείδηση ως βασικής επιστήμης για την υγεία και το «ευ ζην». Στην πορεία ο εορτασμός παγκοσμιοποιήθηκε.

Φέτος, η Ελληνική Εταιρεία Ανοσολογίας διοργανώνει εκδηλώσεις για τον εορτασμό της Ευρωπαϊκής Ημέρας της Ανοσολογίας με έμβλημα ότι:

«η διατήρηση ενός επαρκούς ανοσιακού συστήματος αποτελεί την υποδομή υγιέστερων πολιτών με καλύτερη συνολικά δημόσια υγεία»

Σήμερα, κάτω από τις τρέχουσες κοινωνικοοικονομικές συνθήκες, η επιστήμη της Ανοσολογίας καλείται να επαναπροσδιορισθεί στην επίτευξη του παραπάνω επιδιωκόμενου στόχου, μέσα από αυτό το απλό και ευθύβολο οικουμενικό μήνυμα.

Η Ευρωπαϊκή Ένωση Ανοσολογικών Εταιρειών (EFIS) αργότερα και η IUIS, οι Ευρωπαίοι Ανοσολόγοι, οι Ανοσολόγοι σε ολόκληρο τον πλανήτη, συνεχίζουν να πραγματοποιούν εκστρατεία ενημέρωσης προκειμένου να κάνουν γνωστό στους πολίτες, τον καθοριστικό ρόλο της ανοσολογικής επαγρύπνησης στη δημόσια υγεία.

Οι Ανοσολόγοι μάχονται για την δημόσια υγεία και την ποιότητα ζωής. Ο έλεγχος των λοιμώξεων και η πρόληψη τους, τα αυτοάνοσα νοσήματα, ο καρκίνος, είναι μερικά από τα θέματα που σχετίζονται άμεσα με τη λειτουργία του ανοσιακού συστήματος.

Η Ελληνική Εταιρεία Ανοσολογίας (ΕΕΑ) μέλος της EFIS και της IUIS, συμμετέχει και φέτος επίσημα στον εορτασμό της Παγκόσμιας Ημέρας Ανοσολογίας και οργανώνει ενημερωτικές δραστηριότητες προς το ευρύ κοινό, ώστε η εύρυθμη λειτουργία του ανοσιακού συστήματος να αποτελεί ανάγκη ζωής για τον καθένα μας ξεχωριστά και μοχλό ενίσχυσης της συνολικής προσπάθειας για διαφύλαξη της δημόσιας υγείας.

Ας ενώσουμε όλοι τις προσπάθειές μας σ' αυτόν τον κοινό σκοπό.

Εκ μέρους του ΔΣ της ΕΕΑ

Παναγιώτα Μπούρα
Πρόεδρος ΕΕΑ
Καθηγήτρια Παθολογίας – Κλινικής Ανοσολογίας ΑΠΘ


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ΠΡΟΓΡΑΜΜΑ

ΣΑΒΒΑΤΟ 09 ΑΠΡΙΛΙΟΥ 2016

09:00-10:00 ΕΓΓΡΑΦΕΣ - ΠΑΡΑΛΑΒΗ ΥΛΙΚΟΥ ΣΥΝΕΔΡΙΟΥ

10:00-11:30 ΤΕΛΕΤΗ ΕΝΑΡΞΗΣ

Προεδρείο: **Π. Μπούρα – Α. Νοτόπουλος**

ΧΑΙΡΕΤΙΣΜΟΙ - ΕΙΣΗΓΗΣΕΙΣ

Α. Ξανθός, Υπουργός Υγείας και Κοινωνικής Ασφάλισης
Μ. Κόλλια-Τσαρουχά, Υπουργός Μακεδονίας-Θράκης
Α. Τζιτζικώστας, Περιφερειάρχης Κεντρικής Μακεδονίας
Ι. Μπουτάρης, Δήμαρχος Θεσσαλονίκης
Ε. Πλωμαρίτης, Διοικητής 4ης Υ.Π.Ε. Μακεδονίας-Θράκης

ΠΡΟΣΚΕΚΛΗΜΕΝΗ ΟΜΙΛΙΑ

Α. Τσίπρας, Πρωθυπουργός Ελλάδας

11:30-12:00 ΔΙΑΛΕΙΜΜΑ - ΚΑΦΕΣ

12:00-14:00 ΣΤΡΟΓΓΥΛΗ ΤΡΑΠΕΖΑ:
Πρωτοβουλίες Ιατρικής Φροντίδας σε μια κοινωνία σε διακινδύνευση

Προεδρείο: **Ι. Καμτσίδου – Ε. Πλωμαρίτης – Π. Αβραμόπουλος**

Χτίζοντας ένα λειτουργικό δίκτυο πρωτοβάθμιας φροντίδας υγείας στην Ελλάδα ..... *Α. Μπένος*
Εκκλησιαστική προσέγγιση φροντίδας υγείας σε εποχή κρίσης ..... *Θ. Αποστολίδης*
Δίκτυα αλληλεγγύης προς διασφάλιση της κοινωνικής συνοχής ..... *Χ. Αηδονόπουλος*
Κοινωνικές πρωτοβουλίες παροχής φροντίδας υγείας σε συμπιεζόμενες ομάδες πληθυσμού ..... *J. Wall-Strasser*
Ιδιωτικές πρωτοβουλίες βελτιστοποίησης της υγείας του κοινωνικού συνόλου ... *Κ. Παπαποστόλου*
Αποδόμηση του κοινωνικού κράτους πριν και τώρα ..... *Γ. Δουράκης*
Βυζαντινοί Ξενώνες Υγείας και μηνύματα για σύγχρονες προνοιακές παραμβάσεις ..... *Α. Νοτόπουλος*
Η πάλη για την βέλτιστη φροντίδα υγείας υπό την πίεση της οικονομικής κρίσης ..... *Α. Ξανθός*

14:00-15:30 ΓΕΥΜΑ

15:30-17:30 ΣΤΡΟΓΓΥΛΗ ΤΡΑΠΕΖΑ:
Εργαλεία οργάνωσης και βελτίωση δυνατοτήτων της Υγειονομικής Περίθαλψης

Προεδρείο: **Μ. Χατζηδημητρίου – Α. Ζαπράνης – Ι. Αθανασιάδης**

Ιδιαιτερότητες λειτουργίας των φορέων υγείας σε εποχή κρίσης ..... *Ι. Τζάκη*
Σύστημα Υγείας και Πολιτική Επικοινωνία ..... *Β. Βλασίδης*
Η οικονομική θέση των Νοσοκομείων ως μοχλός ανάπτυξης της έρευνας ..... *Θ. Κοματάς*
Εξελιγμένα δίκτυα στη χρηματοοικονομική της υγείας ..... *Α. Ζαπράνης*
Clouds για την διαχείριση των χρηματοοικονομικών δεδομένων της υγείας ..... *Ι. Ζεμπεκάκης*
Ιατρικός τουρισμός και ανάπτυξη ..... *Τ. Τζιούμης*
Ισορροπία κόστους - αποτελεσματικότητας στο σχεδιασμό πολιτικών υγείας ..... *Ε. Τσακαλώτος*

17:30-18:00 ΔΙΑΛΕΙΜΜΑ - ΚΑΦΕΣ

18:00-20:00 ΣΤΡΟΓΓΥΛΗ ΤΡΑΠΕΖΑ:
Επιστημολογική, Μοριακή και Απεικονιστική προσέγγιση στα άδυτα του εγκεφάλου
Προεδρείο **Χ. Νικολάου – Κ. Πολυζωίδης**

Νευροανοσολογικές αλληλεπιδράσεις ..... *Χ. Νικολάου*
Νευροχειρουργική προσέγγιση στα άδυτα του εγκεφάλου ..... *Χ. Τσονίδης*
Παιχνίδια του νου στο πεδίο της οπτικής αντίληψης ..... *Β. Καραμπατάκης*
Απεικονιστική διερεύνηση εγκεφαλικών λειτουργιών ..... *Γ. Γερασίμου*
Επιστημολογική θεώρηση της ανάδυσης και διαμόρφωσης της συνείδησης ..... *Π. Νοτόπουλος*

ΚΥΡΙΑΚΗ 10 ΑΠΡΙΛΙΟΥ 2016

10:00-11:00 ΣΤΡΟΓΓΥΛΗ ΤΡΑΠΕΖΑ:
Cost-effective Technologies
Προεδρείο: **Κ. Ζαρογουλίδης – Α. Δούμας**

Είναι το PET-CT cost-effective εξέταση; ..... *Β. Πρασόπουλος*
Ελάχιστα επεμβατική (λαπαροσκοπική - ρομποτική) χειρουργική στον καιρό της κρίσης ..... *Κ. Ψαρράς*
Ηλεκτρομαγνητική βρογχοσκόπηση (electromagnetic guidance bronchoscopy) ..... *Σ. Τρύφων*
Ενδοβρογχικός υπερηχογραφικός έλεγχος (EBUS) ..... *Π. Ζαρογουλίδης*

11:00-12:00 ΣΤΡΟΓΓΥΛΗ ΤΡΑΠΕΖΑ:
Επιτεύγματα της Βιοϊατρικής Απεικονιστικής Τεχνολογίας
Προεδρείο: **Α. Δρεβελέγκας – Α. Ζησιμόπουλος**

Πρόοδοι στη μορφολειτουργική απεικόνιση του εγκεφάλου ..... *Α. Φωτόπουλος*
Redefine what is possible - The promise of PET/CT ..... *Ε. Βαρδαλάκη*
Η επιβάρυνση του ελληνικού πληθυσμού από τις ιατρικές εφαρμογές ιοντιζουσών ακτινοβολιών ..... *Μ. Νικολάου*
Επιδράσεις ιοντιζουσών ακτινοβολιών κατά την εγκυμοσύνη και η αιτιολόγηση των ιατρικών εκθέσεων ..... *Σ. Οικονομίδης*

12:00-12:20 ΔΙΑΛΕΙΜΜΑ - ΚΑΦΕΣ

12:20-13:15 ΣΤΡΟΓΓΥΛΗ ΤΡΑΠΕΖΑ:
Πρωτότυπες θεραπευτικές επιλογές
Προεδρείο: **Αικ. Ταράση-Ζαφειροπούλου – Γ. Ευστρατιάδης**

Αποτελεσματικότητα, κόστος, αξία και θεραπευτικές επιλογές ..... *Α. Τσάπας*
Αναγεννητική Ιατρική: Η δύναμη των βλαστικών κυττάρων στην εξατομικευμένη θεραπεία ..... *Ε. Μιχαλόπουλος*
Ανοσοθεραπεία του καρκίνου: Σύγχρονες προκλήσεις ..... *Χ. Εμμανουηλίδης*
Εξατομικευμένη θεραπεία και φαρμακογονιδιωματική: Προοπτικές και προκλήσεις ..... *Ι. Βιζιριανάκης*

13:15-14:00 ΣΤΡΟΓΓΥΛΗ ΤΡΑΠΕΖΑ:
Πρωτότυπες θεραπευτικές παρεμβάσεις
Προεδρείο: **Γ. Μαράκης – Θ. Παυλίδης**

Ρομποτική χειρουργική θώρακα ..... *Δ. Φιλίππου*
Μεταμόσχευση ηπατοκυττάρων ..... *Ι. Φούζας*
Ραδιοεμβολιασμός: Ασφάλεια και αποτελεσματικότητα ..... *Ι. Δέδες*

14:00-15:00 **ΣΤΡΟΓΓΥΛΗ ΤΡΑΠΕΖΑ:**
Η επίδραση της Κοσμικής Ακτινοβολίας στην ανθρώπινη υγεία
Προεδρείο: **Α. Γκοτζαμάνη-Ψαρράκου – Χ. Ανδρεάδης**

Τι είναι η κοσμική ακτινοβολία και γιατί μας ενδιαφέρει; ..... *Δ. Σαρηγιάννης*
Κοσμική ακτινοβολία και ανοσιακό σύστημα ..... *Π. Μπούρα*
Διακυμάνσεις των ορμονών στο διάστημα ..... *Χ. Παπαδέλη*
Ηλεκτρομαγνητική ακτινοβολία και περιβάλλον ..... *Α. Μιζαμίδης*

15:00-16:00 **ΓΕΥΜΑ**

16:00-16:30 Προεδρείο: **Αικ. Σταυροπούλου-Γκιόκα – Αικ. Παυλίτου**

ΠΡΟΣΚΕΚΛΗΜΕΝΗ ΟΜΙΛΙΑ
The mutanome as a biomarker in the era of immune checkpoint inhibitors for cancer treatment ..... *Ι. Θεοδώρου*

16:30-18:00 **ΣΤΡΟΓΓΥΛΗ ΤΡΑΠΕΖΑ:**
Ανοσιακό Σύστημα και Δημόσια Υγεία
Προεδρείο: **Π. Μπούρα – Α. Νοτόπουλος**

Η σημασία της πρόληψης και της επαρκούς ανοσίας στη δημόσια υγεία ..... *Π. Μπούρα*
Ψαχονευροανοσολογία: Εκεί που η Ανοσολογία συναντά την Ψυχιατρική και Νευρολογία ..... *Χ. Νικολάου*
Εξωκυττάρια ουδετεροφιλικά δίκτυα (Neutrophil extracellular traps-NETs): Ένας αναδυόμενος ανοσολογικός μηχανισμός στα φλεγμονώδη νοσήματα ..... *Π. Σκένδρος*
Κριτική ανάλυση θεραπευτικών αλγορίθμων στη Ρευματοειδή Αρθρίτιδα με βάση στοιχεία φαρμακοοικονομίας ..... *Α. Σαραντόπουλος*
Ο ρόλος της ψηφιακής τριχοειδοσκόπησης στη σύγχρονη ιατρική. Σχέση κόστους-οφέλους ..... *Ι. Γκουγκουρέλας*
Ανοσο-PET (Immuno-PET) ..... *Α. Νοτόπουλος*

13:00-14:00 **ΤΕΛΕΤΗ ΛΗΞΗΣ**

ΣΥΜΠΕΡΑΣΜΑΤΑ ΣΥΝΕΔΡΙΟΥ

ΒΡΑΒΕΥΣΕΙΣ ΕΡΓΑΣΙΩΝ

ENMF 2016

The Demolition of the Welfare State in Historical Perspective

G. Dourakis

ανοσία *2016; 12, 1: 22 – 23*

The most obvious feature of the Great Recession from mid-2010 onwards was certainly the explosion of public deficits and debts. During the first two years of the crisis (2008-2009), the risk of an imminent collapse of the global economy had forced governments to step in and spend huge amounts of public money to bail out banks and to support the real economy and employment. The bailout of the financial system with public funds –i.e. the conversion of private sector losses to public losses-, fueled a spectacular growth of public deficits and debts. Confronting a potential fiscal derailment, governments rushed to withdraw their fiscal stimuli and by mid-2010 they began to implement short-term fiscal consolidation policies, i.e. restrictive fiscal policies, combining spending cuts and tax increases. Therefore the price paid by most societies to rescue their banks was a drastic shrinking of the welfare state, mainly in public health and public education.

However the reduction and degradation of the welfare state has deeper causes, which existed long before the onset of the recent economic crisis. Actually this phenomenon began in the early '80s, after the triumph of new economic liberalism and the consolidation of a free market system (laissez-faire), and has since continued unabated. The current economic crisis has just accelerated this process. One of the key strategic objectives of neoliberalism, as expressed by its leading founder Milton Friedman, is the elimination of public goods and their provision by the private sector. So, according to this view, in the long run we do not need to have any public health or public education services. These services can be provided much more effectively and efficiently by private firms. During the long transitional period, the main vehicle for the gradual implementation of the neoliberal strategy is a simple, concise and practical governance formula, known as the "Washington Consensus". The key recommendations of this recipe are extremely simple and clear-cut: deregulation, privatization and drastic reduction of the welfare state. It is a set of economic policies that are now applied in many countries all over the world, no matter how different they are, with the encouragement and the insistence of the IMF and the World Bank.

Unfortunately the crisis has hit our country with an unprecedented ferocity. The annual material and intangible output (GDP) is down by 25%, unemployment has assumed nightmare proportions (varies consistently around 25%), public debt has gone through the roof (it is now exceeding 180% of GDP), while the production capacity continues to decline for the eighth consecutive year! This is a negative peacetime world record, at least as far as it concerns the economic performance of western countries over the past eighty years. And all that happened despite the dramatic decline in the income of the lower and middle classes brought about by the violent fiscal adjustment process.

However the living standards of these social classes were not only directly affected by the reduction of wages, but also indirectly, through drastic cuts in government spending in the areas of health and education. Just when more than ever all these people needed the support of the welfare state to make ends meet, they saw social services shrink and deteriorate considerably. This may have dramatic social consequences. The crisis-induced lack of money is forcing

many people (both insured and uninsured) to reduce their visits to the doctor, not to buy the drugs they need or/and to decrease the necessary preventive examinations. Therefore the chances of serious or chronic diseases increase, which –among other things– would unduly burden the public budget, since their hospital treatment involves much higher costs. There is no doubt that our country should reduce per capita health expenditure, which is too high. The savings, however, should not come from the reduction or degradation of the services provided by the national health system, but from fighting the excessive use of drugs and/or overpricing of all kinds of supplies in the public hospitals. This is an enormous task. It requires political will and effectiveness in fighting corruption, i.e. direct conflict with the powerful interlocking interests in the health sector.

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Byzantine "Xenones" and messages for designing contemporary optimal health care interventions

A.K.C. Notopoulos

ανοσία *2016; 12, 1: 24 – 26*

In ancient Greece, for the first time in history, the Hippocratic Collection of medical texts introduced the rational investigation of the underlying causes of various diseases. It should be noted that the practice of medicine had not yet incorporated the social character and orientation that have later enriched our experience, as it did not constitute an obligation of the state to provide health care. The existing treatments of the patients took place at their home and occasionally they resorted to Asclepieia for sleeping under intentional conditions and curative-mystical-apocryphal interventions.

Well refined conceptions on human brotherhood and the definition of medical profession (towards a sense of a special call or mission of the physician) emerged only in the late antiquity by Skrivonius Largus, Serapion and Soranus from Ephesus. During the Hellenistic and Roman period there are mentioned only a few individual initiatives [i.e. the first orphanage in history made by the emperor Trajan for the children of killed legionnaires (Fig. 1), the military valetudinaria introduced by the emperor Marcus Aurelius for the injured soldiers], reflecting a subtle trend to socialized application of health rules, certainly without any systematization in forms of organized care. The first private medical office ("medical tavernae") in Rome was founded by a Peloponnesian doctor in 219 BC, while in 70 AD the city of Gythion bestowed praise for the chief public doctor because of his diligent care for the poor patients (as this care and liability was not at all expected then).

Inspired by the self-transcendent Christian love (which envisages each patient created as an image and in the likeness of God and considers any offering for him/her as a fundamental issue for the salvation of human beings) and the organizational vigor of the emerging New Rome (i.e. Constantinople), there took place the creation of a network of philanthropic social and health care units, called "xenones", that was further expanded and integrated into the appearance of the first historically certified hospital care provision. While not claiming for innovations in medical practice, the greatest medical achievement of the era is patient care organization. During this period, it became the duty of any believer or citizen to practice charity.

Fig 1. *Plutei of Trajan. A huge marble relief located inside the Curia showing Trajan seating on a podium in the Forum Romanum, instituting the alimenta, a charitable organization for orphans. On his right, there stands a personification of Italia, carrying a child on her arm.*

In 356, Eustathios established "xenodocheion" to care for the sick and the lepers in Sebaste of Armenia, whereas Aetios combined the medical treatment with his clerical activities. In 372, St. Basil of Caesarea created on his own expense a magnificent benevolent complex in his birthplace Caesarea of Cappadocia. The

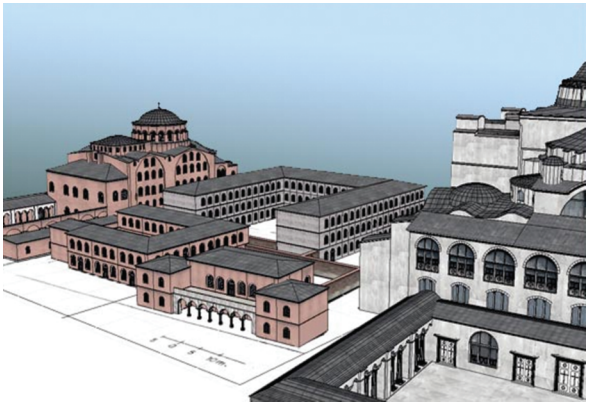

Fig. 2. *Part of a computer reproduction of the Hospital of Sampson lying between St. Sophia and St. Eirene. It was founded in the late 4th century by St. Sampson who housed homeless people and healed the sick ones. It was restored by Justinian after its destruction during the Nika Riot. After St. Sophia, it has been the most brilliant building of Constantinople.*

Vasileiada included the cathedral, the residence of the Bishop, priests' and ministries' houses, hospital, nursing home, orphanage, leper, houses for the medical and nursing staff, hostels for visitors and poor people, technical schools for young, buildings for workshops and domiciles for craftsmen.

Among the plethora of similar institutions, the most distinguished, considering their brilliance and high quality of service, were the Guest House of Sampson since the 4th century (Fig. 2), the Mangana Xenon since the IIth century and the Hospital of the Pantocrator Monastery since the I2th century (Fig. 3). The

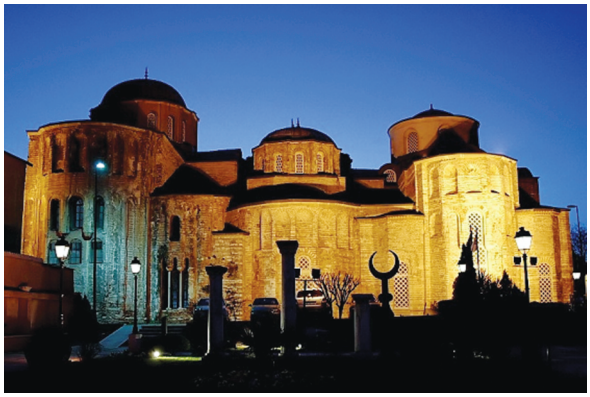

Fig. 3. *The nowadays Zeyrek Camii has formerly been the Pantocrator Monastery with its famous Hospital, founded by the Emperor John II Komnenos and his wife Eirene in 1118-1123. The Hospital was divided in 5 wards, each of them served by 2-3 doctors, 3-4 certified assistants, 2 complementary assistants and 2 nurses. Every detail is reported in Typikon.*

latest's Typical sets impressively every detail of the daily operation of the hospital designed for 50 patients and the nursing home for 24 aged men.

These xenones made a significant contribution to the training of young physicians. Women doctors had an essential role in medical practice. There was a trend for giving special attention to bathrooms ("diakoniai" were specially devoted to provide baths to the poor), heating and cleanliness of patients.

Payments or tips for medical care in xenones were banned. Hospitals supplied clothes and money to the poor patients so that they can cope with their difficulties during the first three months after their hospitalization. The hospital clothing items and linens were renewed every year and the old ones were distributed among the poor people. As we obviously see, some welfare initiatives of that era still remain as enviable and unsatisfied demands for our current season. With this level of active function, apart from taking care of and curing the needy patients, the hospitals gradually started to appeal to the aristocracy and became an attractive place even for the cure of the imperial families.

The xenones were operating depended on the financial support of the imperial government, the Church and some monasteries, the donations of wealthy families, the low paid medical work and the bequests made by benefited patients. Their creation does not appear to be the result of a systematic plan (i.e. recording or predicting the needs to be anticipated, creating social awareness that treatment is an individual right of every citizen), but it springs from the Christian compassion for the dynamic response to the increased needs of the social body, exacerbated by the continuous wars, the great migration waves, the epidemics, hunger periods, etc.

The Christians doctors – through their personal transformation – adopt such anthropological presuppositions, that they show a rather abundantly flourishing than conformational way of life, providing conscious, selfless and loving service to their fellow human beings in response to divine calls, which activate their constitutive inner appeals.

Gradually the consolidation of the institution, led the Emperor Justinian (6th century) in the drafting of detailed legislation for such institutions, considering that xenones and Hospitals help each city to obtain its appropriate form. This view was further enhanced by the wise counselor Theodore Metochites (in the years of the Empire of Nicaea), adding the missing completeness into the ancient Greek concept of the

city. This network of xenones and hospitals provided treatment to the hospitalized patients as well as walk-in clinical services and medicines to the general population.

Justinian (and later Leo III the Isaurian) determined legally the right of any citizen to intervene when a hospice or hospital failed to perform its social function. The self-regulation bestowed to these institutions enabled their effective development and gave a Christian channel expressing the ancient Greek spirit of sponsorship. These institutions incorporated the civil chief doctors (municipal archiatroi) who were transferred from the payroll of the cities to the staff of the xenones. Gradually, every doctor acquired fame through their work into them in monthly shifts (eg in the Hospital of the Pantocrator Monastery, doctors worked every other month, earning very low salaries, while in the intermediate periods they were allowed to practice their own private profession, charging a rather high price for their visits).

With regular benefits from the public treasury and tax breaks, the operation of these xenones continued, nevertheless constantly albeit with fluctuations, even in difficult times of crisis – which forced the elimination of the governmental support of the institutions – still functioning through private donations during the end of the Empire.

Indeed, they gave rise to the first hospitals of the Persian Empire (in Tzountisapour by Nestorian monks), the Muslim patients' homes (bimaristans) and the Western hospitals of monastic orders initially.

Today, in an era of heightened economic compression and mitigation of social solidarity disposal, wherein the expression of the reasonable human feelings is determined and counterbalanced by certain financial parameters, our reference to the experience of the first historical and very extensive, though not systematic, social welfare and organized patient care in a society embedded with a different perception of state and personal perspectives, enriches the demanded rational planning with aspects of action particularly impressive and consolidates the sense of responsibility for optimizing the current welfare interventions.

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ΕΝΜΦ 2016

Σύστημα Υγείας και Πολιτική Επικοινωνία

Β. Βλασίδης

ανοσία *2016; 12, 1: 27*

Η υγεία σε όλες τις κοινωνίες και σε όλες τις εποχές θεωρείται υπέρτατο αγαθό. Το ίδιο και στην Ελλάδα. Γι αυτό το λόγο όσοι εμπλέκονται στο σύστημα παροχής υγείας παραδοσιακά απολάμβαναν ένα ιδιαίτερο καθεστώς σε σχέση με τα υπόλοιπα μέλη της κοινωνίας. Αυτοί ήταν που μπορούσαν να διατηρήσουν ή να εξασφαλίσουν το υπέρτατο αγαθό, την υγεία. Επιπλέον οι νέες ανακαλύψεις στην ίαση των παθήσεων, οι χειρουργικές επεμβάσεις και οι θεραπείες μέσω μηχανημάτων δημιουργούσαν στο κοινό μια αίσθηση ασφάλειας απέναντι σε πιθανούς κινδύνους. Ταυτόχρονα οι ειδήσεις σχετικά με τις νέες επιστημονικές ανακαλύψεις πάντα προσέλκυαν το ενδιαφέρον του κοινού, είτε σε πραγματική βάση, είτε στη σφαίρα του ιδεατού ή του απίθανου, που όμως πλέον περνούσε στο επίπεδο της απλής πραγματικότητας για τους ασθενείς και της ρουτίνας για το ιατρικό προσωπικό.

Η οικονομική κρίση στην Ελλάδα άλλαξε τον τρόπο με τον οποίο αντιμετωπίζουμε την υγεία, τους γιατρούς, τα νοσοκομεία και τις επιστημονικές ανακαλύψεις. Η αδυναμία εργασίας έχει ωθήσει μεγάλο μέρος των Ελλήνων στο περιθώριο και οι οποίοι, αν και έχουν εξασφαλισμένη ακόμη την πρόσβαση στις υπηρεσίες υγείας, ωστόσο αισθάνονται αδικημένοι απέναντι σε όλους τους άλλους που απολαμβάνουν των κανονικών υπηρεσιών. Υπάρχει πλέον αμφιθυμία και καχυποψία, ίσως και ζήλια.

Επιπλέον η ημερήσια διάταξη (το agenda setting) των μέσων ενημέρωσης) έχει αλλάξει. Η περιστολή δαπανών έχει την πρωτοκαθεδρία και οι κυβερνώντες, οι όποιοι κυβερνώντες, δίνουν στη δημοσιότητα τις περιπτώσεις σπατάλης κατά το παρελθόν, ώστε να πετύχουν πιο εύκολα τη συναίνεση στην περιστολή των δαπανών στην υγεία συνολικά, ή στην διακοπή παροχής υπηρεσιών. Οι τηλεθεατές, οι ακροατές νομίζουν ότι η εξαίρεση του κανόνα, ήταν ο κανόνας, επομένως τείνουν να αντιμετωπίζουν πλέον εχθρικά την παροχή υπηρεσιών υγείας και το ιατρικό προσωπικό στο σύνολό του. Επιπλέον άτομα που χρήζουν μακρόχρονης και σταθερής θεραπείας, που βλέπουν την περιστολή των δαπανών για την περίπτωσή τους, όχι μόνο δεν απολαμβάνουν τη συναίνεση της κοινωνίας, αλλά αντιμετωπίζονται επικριτικά. Αντί να τους αντιμετωπίζουν ως χρόνια ασθενείς, τους αντιμετωπίζουν ως κλέφτες του δημόσιου χρήματος.

Είναι φανερό ότι τα μέσα ενημέρωσης χρησιμοποιήθηκαν κατά τη διάρκεια της κρίσης (2010-2016 κ.ε.) ως όργανα διαχείρισης του κοινού, προκειμένου να πετύχουν πιο εύκολα τις περιστολές στο σύστημα απονομής περίθαλψης και εξασφάλισης της υγείας. Ο στόχος επετεύχθη και πλέον το κοινό στρέφεται επικριτικά προς όσους «σπαταλούν» το δημόσιο χρήμα, νοσηλευτικά ιδρύματα, εταιρείες, ιατρικό και νοσηλευτικό προσωπικό και ασθενείς. Όμως με αυτό τον τρόπο τραυματίζουν το σύνολο του συστήματος, και το ωθούν σε χειρότερες επιδόσεις στο μέλλον.

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The German Health Care System – Commercialized health care is rather expensive and bad for patients and employees

Rakowitz Nadja

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Since the beginning of the 1990ies we are facing the commercialization of the German Health Care System. The social health insurances have not been privatized by being sold to a company but they have been "reformed" from inside by adapting most of the principles of private insurances. Before the 1990ies the hospitals in Germany were either public or independent non-profit. Now more than 30% of the hospitals are privately operated for example by Fresenius Helios, one of the 30 top companies on the German stockmarket. But the other ones are also forced to operate similar to the private owned and profit driven hospitals.

The changes in hospital reimbursement with the mandatory introduction of the DRG system in 2004 brought dramatic changes in the hospital surgery: On one side reduction in the average length of stay and cost transparency, on the other side reduction of nurses (one nurse for 35 freshly operated patients at night is "normal" in German hospitals) and an increase in "productivity" (less employees for more patients with shorter length stay). But the worst consequence of the DRGs is the decline of medical services. Procedures and therapies are driven by economic principles not by medical criteria. But even the economical goal of cost reduction was not fulfilled. Costs are rising faster than before.

While in Germany a movement against DRG and the commercialization of health care is starting to grow the 3rd Memorandum still wants Greece to implement (German) DRGs and reorganize hospitals in line with the German "model" – a model of the most commercialized health system in Europe!

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Τουρισμός και Υπηρεσίες Υγείας. Παρούσα κατάσταση και διερεύνηση των δυνατοτήτων παροχής ιατρικών υπηρεσιών σε μονάδες υγείας της Βορείου Ελλάδος για την ανάπτυξη του τουρισμού

Τ. Τζιούμης

ανοσία *2016; 12, 1: 29*

In the last three decades a change has occurred in the preferences of travelers, which concluded in the comeback of health tourism, a very popular form of tourism since antiquity. There is a presentation of the historical evolution of the phenomenon, up to our days.

This presentation is about health tourism in a theoretical basis, in an attempt to recorf it's sub - categories, to set the limits of it's market and in general to define all the determinative factors of the phenomenon. There is also a presentation of medical health destinations that have already met growth of this sector or with common characteristics with North Greece.

There is also reference, to one of the main reasons for medical tourism growth globally, which is the variance of price for medical services, among the healthcare systems and the private providers. There is mentioned a coding and categorizing system of diseases and treatments that have been accepted globally, for the cost control in healthcare services. Examples of pricing are given, in combination with necessary synergies and co-operations.

Additionally through a SWOT analysis, the presentation focuses on the estimation of medical tourism's chances of development in North Greece and the possibility of basing this development, on the offering of medical services in existing healthcare units.

Furthermore, there is an attempt to study the healthcare units through a first degree research with the top executives that manage them. This way, an assessment for Health Tourism itself and for the ability of its growth in this certain region, is produced.

At the end, the goal of this presentation is the recording of the theoretical framework for health tourism and the utilization of the extracted results in creating the proper strategy for the development of health tourism in North Greece, focused in the prefectures of Thessaloniki and Chalkidiki, through certain propositions.

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Visual brain games

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The visual signals are transmitted to the visual cortex and are followed by the analysis of their components in various brain centers. The process targets to the perception and understanding of the optical information and the individuals perceive the image, the light and its intensity, the colors, the shapes and the size, as well as the distance and the mobility of the objects and creates a complete live picture of the surroundings. Further evaluation of the environment is related to higher sensory, emotional and cognitive functions as the visual stimulus is finally integrated triggering the relative individual responses. Former visual experiences, memory records and emotional responses to the stimulus are linked accordingly completing the visual function. In this path of vision related brain processes, a deviation may happen producing a faulty visual perception.

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Η απεικόνιση των εγκεφαλικών λειτουργιών

Γ.Π. Γερασίμου

ανοσία *2016; 12, 1: 31*

Η φιλοδοξία των νευρο-επιστημόνων στο να κατανοήσουν τον εγκέφαλο και τις λειτουργίες του, έχει συναρπάσει πολλούς. Σήμερα είμαστε στην ευχάριστη θέση να το επιτύχουμε πραγματικά, με την βοήθεια των σύγχρονων τεχνικών εγκεφαλικής απεικόνισης, όπως είναι οι τεχνικές της Ακτινολογίας (λειτουργικό MRI) και της λειτουργικής-μοριακής απεικόνισης με μεθόδους της Πυρηνικής Ιατρικής (SPECT και PET).

Η ανατομική απεικόνιση των δομών του εγκεφάλου με τη μαγνητική τομογραφία, επιτρέπει την διερεύνηση των ελίκων και αυλάκων, των λεπτών δομών και των σχηματισμών της φαιάς και λευκής ουσίας με υψηλή διακριτική ικανότητα.

Τα τελευταία χρόνια έχει εξελιχθεί το λειτουργικό MRI (fMRI), το οποίο βασίζεται στη διαφορά των μαγνητικών ιδιοτήτων της οξυαιμοσφαιρίνης και της μη οξυγονωμένης αιμοσφαιρίνης στο αίμα.

Με την λειτουργική απεικόνιση με τη μέθοδο SPECT χρησιμοποιώντας λιποφιλικό παράγωγο (HMPAO) επισημασμένο με μετασταθερό τεχνήτιο (Tc-99m), επιτυγχάνεται η χαρτογράφηση της τοπικής αιματικής εγκεφαλικής ροής (rCBF), ενώ επιπλέον, είναι εφικτή και η σύνδεση των λειτουργικών παραμέτρων του εγκεφάλου (μνήμη, προσανατολισμός, πράξη, λόγος), με τις τυχόν μεταβολές της εγκεφαλικής άρδευσης.

Η λειτουργική απεικόνιση με ποζιτρονιακή κάμερα (PET) χρησιμοποιείται για τη χαρτογράφηση μεταβολών στην rCBF και στον μεταβολισμό της γλυκόζης, αλλά και στη συμπεριφορά νευροδιαβιβαστών. Χρησιμοποιούνται βραχύβια ραδιοφάρμακα παραγόμενα από κυκλοτρόνιο. Τέτοιες μετρήσεις οδήγησαν στον εντοπισμό αισθητικών, κινητικών και γνωσιακών λειτουργιών στον ανθρώπινο εγκέφαλο.

Στις SPECT και PET μελέτες χρησιμοποιείται το μοντέλο της στατιστικής παραμετρικής χαρτογράφησης (SPM), το οποίο συνίσταται στην επιπροβολή των λειτουργικών μεταβολών στο ανατομικό μοντέλο του εγκεφάλου.

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Endobronchial ultrasound (EBUS)

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ανοσία *2016; 12, 1: 32 – 33*

Endobronchial ultrasound (EBUS) is a technology that allows real-time visualization of structures adjacent to the airways during bronchoscopy. Linear EBUS incorporates an ultrasound transducer into the tip of a standard bronchoscope and guides transbronchial needle aspiration (TBNA) of lymph nodes and parabronchial masses. Radial EBUS integrates a miniature ultrasound transducer into a free-standing probe that can be advanced through the bronchoscope's working channel into the periphery of the lung to guide sampling of peripheral lung nodules and masses. EBUS was introduced into bronchoscopy almost a decade ago and has transformed the diagnostic approach to mediastinal and hilar diseases, particularly in lung cancer. The American College of Chest Physician's (CHEST) Lung Cancer Guidelines, third edition, summarized the data on EBUS-TBNA in the mediastinal staging of lung cancer and reported an overall median sensitivity of 89% and median negative predictive of 91%.[1,2,3] Based on these findings, these guidelines recommended ultrasound-guided needle-based sampling techniques over surgical staging as the first step in the mediastinal staging of lung cancer. Additionally, EBUS can be used for visualization of thrombus inside vessels, local therapy application (tumor/lymph nodes), measurement of pulmonary hypertension and pericardial effusion aspiration.[3,4]

Recommendations for the EBUS diagnostic technique

1. In patients undergoing EBUS-TBNA, we suggest that either moderate or deep sedation is an acceptable approach (Grade 2C).

2. In patients undergoing EBUS-TBNA, we suggest that ultrasonographic features can be used to predict malignant and benign diagnoses, but tissue samples should still be obtained to confirm a diagnosis (Ungraded Consensus-Based Statement).

3. In patients undergoing EBUS-TBNA, we suggest that tissue sampling may be performed either with or without suction (Ungraded Consensus-Based Statement).

4. In patients undergoing EBUS-TBNA, we recommend that the use of either a 21- or 22-gauge needle is an acceptable option (Grade 1C).

5. In the absence of rapid on-site evaluation in patients suspected of having lung cancer and undergoing EBUS-TBNA for diagnosis, we suggest that a minimum of 3 separate needle passes be performed per sampling site (Ungraded Consensus-Based Statement).

6. In patients undergoing EBUS-TBNA for diagnostic evaluation, we recommend that tissue sampling can be performed with or without rapid on-site evaluation (Grade 1C).

7. In patients undergoing EBUS-TBNA for the diagnosis and/or staging of suspected or known non-small cell lung cancer, we recommend that additional samples, beyond those needed to establish the diagnosis, be obtained for molecular analysis (Grade 1C).

8. In training EBUS-TBNA operators, we suggest that low- or high-fidelity simulation be incorporated in training (Grade 2C).

9. In evaluating EBUS-TBNA operators, we suggest that validated EBUS skills assessment tests be used to objectively assess skill level (Ungraded Consensus-Based Statement).

10. In patients with suspected sarcoidosis with mediastinal and/or hilar adenopathy, we recommend that EBUS-TBNA be used for diagnosis (Grade 1C).

11. In patients with suspected tuberculosis with mediastinal and/or hilar adenopathy who require lymph node sampling, we recommend that EBUS-TBNA be used for diagnosis (Grade 1C).

12. In patients with suspected lymphoma, we suggest that EBUS-TBNA is an acceptable initial, minimally invasive diagnostic test (Ungraded Consensus-Based Statement).

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Electromagnetic Navigation Bronchoscopy

S. Tryfon

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Peripheral pulmonary lesions (PPLs) are common incidental findings. Their rising incidence has paralleled the increasing use of computed tomography (CT) as CT is approximately three times more sensitive than plain chest radiography scans.

The diagnostic yield of flexible bronchoscopy is expected to be between 20 and 84% but for lesions less than 2 cm in diameter, is fallen to 14%. The **Electromagnetic Navigation Bronchoscopy** (ENB) system is a new technology that provides navigational assistance coupled with steering ability to localize and sample PPLs. Initial human trials occurred in 2005 and over 20,000 procedures have since been performed.

The system consists of: iLogic virtual bronchoscopy planning software; a "location board" which emits low frequency electromagnetic waves; an extended working channel that is similar in function to a guide sheath; an eight way steerable catheter to enable selective cannulation of bronchi; and a "locatable guide" containing sensors that allow precise tracking of both position and orientation throughout the electromagnetic field.

Preparation and execution of ENB procedures involves several phases: Planning phase; Procedure; Navigation; Sampling (Figure 1).

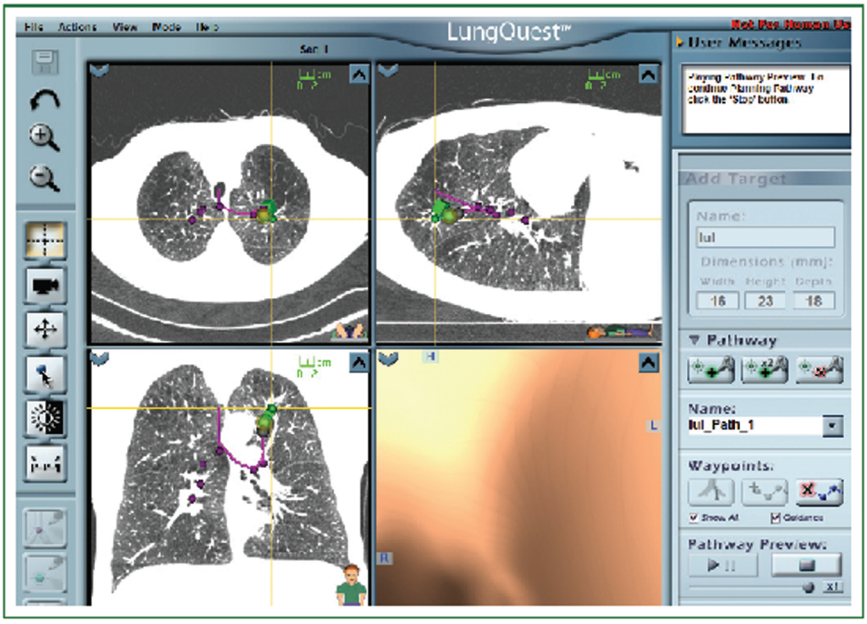

Figure 1. *iLogic virtual bronchoscopy pre-planning screen. Note four viewports showing axial, coronal and sagittal CT views and virtual bronchoscopy view. Green sphere represents the target lesion, the Purple line indicates mapped pathway and purple dots represent anatomical registration points.*

Electromagnetic navigation bronchoscopy is gaining increasing acceptance as a diagnostic modality, particularly in North America and Europe. The overall published diagnostic yield for ENB alone is highly variable and ranges between 59% to 77.3%.

Currently, high level evidence underpinning the technique is limited and its position in the diagnostic algorithm of PPLs remains unclear. Despite the misdiagnostics challenges together with high cost and learning curve, the navigational ability of ENB offers the potential for wider clinical applicability, both diagnostic and therapeutic, than is possible with conventional bronchoscopy.

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Minimally invasive surgery (Laparoscopic & Robotic) in a time of economical crisis

K. Psarras

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In the last three decades, technological advances in optical fibers and robotics have pushed surgical techniques in the era of minimal invasive procedures, such as endoscopic, thoracoscopic, laparoscopic and robotic operations. New indications and guidelines have been published by international surgical societies and are now being consistently followed by surgeons in most developed countries. Open surgical procedures tend to become a historical past in many diseases, or be reserved for complex or complicated cases. Although this offers a great deal in smaller surgical trauma, less postoperative pain, shorter hospital stay, lower incidence of postoperative complications and reoperations, it certainly involves more costly equipment and raises dilemmas if the Health System can afford or is worthy to pay such amounts of money in all cases.

Laparoscopic cholecystectomy was the first minimally invasive procedure to be adopted in the early 90's in our University Hospital and ever since surgeons rushed to attend postgraduate courses in leading countries in order to get acquainted with newer laparoscopic procedures. However, after the onset of economical crisis in Greece, restrictions in materials and instruments have rendered laparoscopic operations from difficult to "dangerous". For example, the laparocopic apparatus tower and cameras that we currently use date back to the early 90's, are old models that have been repaired several times and never been replaced, besides the cameras are two-dimensional with poor quality of vision. We many times get troubled with screen black-outs in the middle of the operation. Three-dimensional cameras are safer, are needed to perform complex manipulations and are those currently used in developed countries. The multiple-use laparoscopic instruments that we have are also old, and do not perform properly. For example scissors fail to cut and "bite" tissues or graspers fail to grasp adequately. Single-use instruments provided on the other hand are the cheapest ones in the market, with low quality performance. Consequently, the laparoscopic surgeon in our University Hospital today makes a scary effort to adopt, and sometimes risks finishing the operation in a marathon of technical problems.

On the other hand and according to the international guidelines, laparoscopic colectomies are now the gold standard operation for colon and rectal cancer in developed countries. This is in other words the commonest operation for the commonest cancer in the Western World. The cost for such a procedure appears higher in first sight and permission to get the specific instruments is prohibitive by hospital authorities. Consequently, none of our five University Departments of Surgery in our city performs this operation today. However, scientists in the US have estimated that the overall cost including longer hospital stay, complications and all medications, is about 6.500$ higher in open procedures.

Robotic surgery has been developed for miniscule manipulations in areas where the anatomy implies very attentive movements, such as in the pelvis or in the heart. However our University does not have any robotic surgery system in any of our hospitals. On the contrary, in private clinics, robotic systems exist, and insurance pays a part at least of the expenses.

Talking about advanced surgical procedures in a time of economical crisis and difficulties that we surgeons face every day in favor of patients' health, we cannot omit to mention that even simple materials such as sutures and gloves that we use today are the cheapest quality in the market. These, as all other materials, are selected through an official procedure (auctional competition) according to their cost, provided that they all appear to have the required specifications. However, for many of them, quality is very poor. Sometimes we need to change gloves 3-4 times because they get easily torn, or use 2-3 different sutures because they get easily broken when tied. It seems that some companies unfortunately pass their quality controls with ambiguous procedures. It would be better after all to buy materials which are a little more expensive but with better quality, or from well known companies in the medical world.

Conclusively, and because in human life our health and safety is the most important gift, our Health Minister officials should reconsider their budgets and their auctional competitions in providing materials and instruments in hospitals in a more scientific and wise way, in order to facilitate surgeons to perform elegant operations in favor of patients.

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Πρόοδοι στη μορφολειτουργική απεικόνιση του εγκεφάλου

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ανοσία *2016; 12, 1: 38*

Η αξονική (ΑΤ) και η μαγνητική τομογραφία (ΜΤ) αποτελούν την εξέταση εκλογής για την ανάδειξη και διαφοροδιάγνωση εξεργασιών του εγκεφάλου. Ωστόσο, δεν παύουν να αποτελούν μια ανατομική απεικόνιση. Οι νεότερες τεχνικές της ΜΤ όπως διάχυσης, αιματικής διήθησης και φασματοσκοπίας προσφέρουν πολλές πληροφορίες για την κατανόηση της παθοφυσιολογίας των όγκων. Η τομογραφική απεικόνιση εκπομπής μονήρους φωτονίου (single-photon emission tomography – SPECT) και η τομογραφία εκπομπής ποζιτρονίου (positron emission tomography – PET) προσφέρουν το μεταβολικό προφίλ αυτών των χωροεξεργασιών. Το PET, παρ' όλα αυτά, δεν είναι ακόμα ευρέως διαδεδομένο και κάθε εξέταση έχει μεγάλο κόστος. Η SPECT σπινθηρογράφηση, από την άλλη, έχει αποδειχθεί ότι αποτελεί μια πολύ καλή εναλλακτική λύση. Η χρήση της SPECT σε χωροκατακτητικές εξεργασίες εγκεφάλου έχει αποφέρει σημαντική βοήθεια σε πολλούς τομείς. Το ραδιοϊσότοπο ^{99m}Tc-Tetrofosmin (^{99m}Tc-TF) είναι ένα ογκόφιλο ραδιοφάρμακο, που αρχικά χρησιμοποιήθηκε στην απεικόνιση της αιμάτωσης του μυοκαρδίου. Στον εγκέφαλο έγινε δυνατή η διάκριση των χαμηλής από υψηλής κακοήθειας όγκων με βάση το βαθμό πρόσληψης της ^{99m}Tc-TF. Επιπλέον, ο βαθμός πρόσληψης του ραδιοφαρμάκου βρέθηκε να σχετίζεται στατιστικά σημαντικά με το δείκτη κυτταρικού πολλαπλασιασμού MIB-I/Ki-67 των γλοιωμάτων. Ιδιαίτερα σε ασθενείς με πολύμορφο γλοιοβλάστωμα, την επιθετικότερη μορφή γλοιώματος με μέση επιβίωση ενός έτους, ο προεγχειρητικός βαθμός πρόσληψης του ραδιοφαρμάκου έχει προγνωστική αξία. Αντίστοιχα σε μηνιγγιώματα με την χρήση της ^{99m}Tc-TF βρέθηκε στατιστικά σημαντική συσχέτιση μεταξύ του βαθμού πρόσληψης του ραδιοφαρμάκου και του MIB-I/Ki-67 καθώς και του ποσοστού της S φάσης των καρκινικών κυττάρων και της ύπαρξης ή όχι ανευπλοειδίας στα μηνιγγιώματα. Επίσης ήταν δυνατή η διάκριση των τυπικών από τα κακοήθη μηνιγγιώματα. Ένα επίσης ιδιαίτερα σημαντικό κλινικό πρόβλημα σε ασθενείς με γλοιώματα που έχουν αντιμετωπιστεί με ακτινοθεραπεία και χημειοθεραπεία είναι η διάκριση της ακτινονέκρωσης από την υποτροπή, μιας και οι δύο οντότητες έχουν πολύ διαφορετική αντιμετώπιση και πρόγνωση. Για την περαιτέρω επιβεβαίωση της τεχνικής επίδοσης (technical performance) καθώς και της διαγνωστικής ακρίβειας (diagnostic accuracy) του Tc-99m tetrofosmin/SPECT, βρίσκεται σε εξέλιξη ένα πρόγραμμα κλινικής ανάπτυξης στα πλαίσια του ερευνητικού έργου «GLIOMARK: Validation of blood-brain-barrier permeability as a glioma biomarker by means of the radiotracer 99mTc-tetrofosmin and single-photon emission computer tomography»* [Horizon 2020-SME Instrument Phase 2].

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* Το παρόν ερευνητικό έργο λαμβάνει χρηματοδότηση από το πρόγραμμα "Ορίζοντας 2020" (Horizon 2020) της Ευρωπαϊκής Επιτροπής για την υποστήριξη καινοτόμων μικρομεσαίων επιχειρήσεων, με αριθμό συμβολαίου No 673737.

Το παραπάνω κείμενο εκφράζει τις απόψεις των συγγραφέων και ο φορέας χρηματοδότησης δεν είναι υπεύθυνος για οποιαδήποτε χρήση της πληροφορίας που περιέχεται ανωτέρω.

Redefine what is possible - The promise of PET/CT

Ε. Βαρδαλάκη

ανοσία *2016; 12, 1: 39*

Η απεικονιστική αξία του PET/CT στην ογκολογία είναι ευρέως αναγνωρισμένη, από την διάγνωση και την σταδιοποίηση, έως τον έλεγχο της αποτελεσματικότητας στην ακτινοθεραπεία, το PET/CT παρέχει στους ογκολόγους –και όχι μόνο– τα δεδομένα για να αποφασίσουν την αποτελεσματικότερη θεραπεία για κάθε περίπτωση.

Παρόλα αυτά ακόμα και σήμερα το PET/CT έρχεται αντιμέτωπο με προκλήσεις, από την αναγκαιότητα της μείωσης της χορηγούμενης δόσης στον ασθενή, μέχρι την απαίτηση για μεγαλύτερη ποσοτική ακρίβεια χωρίς όμως να θυσιάζεται οποιαδήποτε διαγνωστική ικανότητα και ακρίβεια.

Η μείωση της δόσης σήμερα είναι απαραίτητη για κάθε ασθενή, αλλά μείωση δόσης σημαίνει αύξηση του θορύβου, μειώνοντας την ποιότητα της εικόνας οδηγώντας στο χειρότερο σενάριο σε μη διαγνωστική εικόνα. Προκειμένου να μειωθεί ο θόρυβος είτε αυξάνεται ο χρόνος της εξέτασης (αυξάνοντας όμως τις πιθανότητες για εμφάνιση ψευδοεικόνων κίνησης), είτε με το να συλλεχθούν περισσότερες κρούσεις αυξάνοντας την ευαισθησία του μηχανήματος. Η τάση σήμερα στο PET/CT είναι να μπορεί να ορισθεί ποσοτική εκτίμηση της ασθένειας, το οποίο βασίζεται στην τυπική τιμή πρόσληψης SUV (Standard Uptake Value), προκειμένου να διαπιστώνεται νωρίς η αποτελεσματικότητα της θεραπείας που λαμβάνει ο ασθενής. Επομένως η ακρίβεια του SUV είναι πολύ σημαντική.

Άρα πρέπει να είμαστε σε θέση να εξασφαλίσουμε χαμηλής δόσης εξέταση με εξαιρετική ακρίβεια SUV. Τελικά πως είμαστε σε θέση να αντιμετωπίσουμε αυτήν την πρόκληση?

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Estimation of the collective effective dose to the Greek population from medical exposures

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Introduction

Medical exposures contribute the largest to the population man-made radiation exposure, mainly due to the high frequency of diagnostic examinations and the patient doses involved. Greek Atomic Energy Commission (EEAE) estimates the annual collective effective dose and per caput dose to the Greek population from x-ray and nuclear medicine procedures. This work was performed in the framework of 'PRISMA' project within GSRT's KRIPIS action, funded by Greece and the European Regional Development Fund of the EU under the O.P. Competitiveness and Entrepreneurship, NSRF 2007-2013.

Method

The estimation of the annual collective effective dose, S, (person-Sv) and per caput dose, $E_{per\text{-}caput}$, (mSv/caput) requires information on the frequency (i.e. annual number) and the mean patient effective dose, E_{pat}, (mSv) for each type of diagnostic and interventional procedures. The frequency was assessed by a nationwide survey that has been conducted in all radiology and nuclear medicine departments. The E_{pat} was evaluated from dose measurements performed by EEAE and by using appropriate software or ICRP published conversion factors.

Results

In 2014, approximately 6.7 million diagnostic and interventional procedures were performed in Greece. Plain radiography constituted of about 60% of all procedures. The estimated frequency, i.e. number of procedures per 1,000 citizens was: 447 for plain radiographies, 135 for computed tomography scans, 7 for interventional procedures, 2 for fluoroscopic procedures and 20 for nuclear medicine procedures. The annual collective effective dose was estimated to 19776 person-Sv. The annual effective dose per caput was estimated to 1.7 mSv from diagnostic radiology and 0.1 mSv from nuclear medicine procedures.

Conclusions

CT scans contributed 80% of the collective dose from all diagnostic procedures. The frequency and the mean effective dose of plain radiography and mammography were similar or lower compared to relevant data from European countries, while the mean effective dose of CT scans was higher than that of the European average.

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Medical exposures to ionizing radiation during pregnancy

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Often, pregnant women may be exposed to ionizing radiation, either intentionally for medical therapeutic or diagnostic (radiology or nuclear medicine) purposes or sometimes unintentionally. This is an issue that requires special attention and handling due to the increased interest in the doses expected to be received by the fetus.

Special guidelines and reports have been published by scientific organizations and committees concerning the exposure of the fetus to ionizing radiation, as well as the associated risk for the appearance of any biological effects. In some cases fetal doses are not negligible, especially when the fetus lies within the irradiation beam during high dose medical procedures such as computerized tomography (CT) examinations, interventional radiology procedures and radiotherapy.

If the medical exposure is justified and the pregnancy has been confirmed, then certain and adequate measures for the optimization of fetal exposure are required. If the pregnancy has not been confirmed, a thorough investigation is required before a woman at reproductive age undergoes any diagnostic or the therapeutic procedure in order to avoid inadvertent fetal exposure.

For exposures taking place during the first two weeks post-conception no further consideration is needed. After this period, an evaluation of fetal dose is required based on the type of the diagnostic or therapeutic procedure performed. If the evaluation results show that the fetal dose is higher than 100mSv, a further analytical and case by case estimation is necessary regarding the dose and the associated risk. Fetal doses above 100mSv are unlikely to occur due to common medical diagnostic exposures.

EEAE has established a special committee to deal with situations of fetal exposure to ionizing radiation. The role of the committee is mainly consulting. Pregnant women can contact EEAE in order to be informed about the effects of ionizing radiation during pregnancy and to be assisted in decision making.

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Regenerative Medicine: The power of Stem Cells to Personalized Medicine

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The field of regenerative medicine is dedicated to the study of repairing, replacing, or regenerating damaged human cells, tissues, or organs to restore or establish normal function. This could be approached through numerous strategies, from stimulating endogenous processes to repair damaged tissue to deriving or transplanting entire organs to replace those that are beyond endogenous repair[1]. Though the field is currently in its infancy, regenerative medicine is predicted to be one of the most important disciplines in medicine to develop in the next decade, with therapeutic applications in a wide variety of medical conditions. Potential cells that could serve as source materials for regenerative medicine and cellular therapies include hematopoietic stem and progenitor cells derived from bone marrow (BM) or umbilical cord blood (CB), placental and amniotic fluid and tissues, mesenchymal stromal cells (MSCs), skin cells, and other organ-specific cells that could be engineered to perform reparative functions[2].

In the modern era of genomics, systemic and molecular biology, great advances have enhanced knowledge and understanding of disease pathophysiology. New biological markers help early diagnosis and play an important role in decision-making regarding the treatment. Additionally, new technologies allow to better understand the differences between individual cases, a fact that could ultimately lead in the establishment of tailored and personalized treatment to each patient. This, however, has increased the scientific demand for access to high-quality material and information, in order to further advance research and therapeutic applications. Therefore, Biobanks have been created to assist medical research, clinical, and translational medicine. Depending on their purpose and specialty, they are classified into different types. Disease oriented, population based, case control are but some examples of existing Biobanks[3].

Therefore, it will be necessary for clinical grade stem cells to be isolated and maintained in conditions that are established under good manufacturing practices in order to improve, not only survival, but also the therapeutic potency of the cells. In conclusion, in an era where stem cells and the growing field of regenerative medicine elicit excitement and anticipation across the scientific world, it seems appropriate to reconsider the potential future of progenitor cells biology, transplantation, and banking[4].

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Ανοσοθεραπεία του καρκίνου: Σύγχρονες προκλήσεις

Χ. Εμμανουηλίδης

ανοσία *2016; 12, 1: 43*

Η αντίληψη ότι θα μπορούσε η άμυνα του οργανισμού να στραφεί αποτελεσματικά κατά του καρκίνου είναι πολύ παλιά. Ξεκίνησε ως πυρετοθεραπεία πριν από έναν αιώνα, όπου η πρόκληση σηψαιμίας και η εξ αυτής διέγερση του ανοσοποιητικού μπορούσε να βελτιώσει κάποιους μεταστατικούς καρκίνους και συνεχίστηκε με την χορήγηση του βακίλου BCG για την πρόληψη τοπικών υποτροπών καρκίνου της κύστεως. Κατόπιν, στην δεκαετία του 60 η ανακάλυψη των κυτοκινών όπως η ιντερφερόνη και η ιντερλευκίνη προκάλεσαν μεγάλο ενθουσιασμό ο οποίος σύντομα περιορίστηκε στην μικρή κλινική χρησιμότητα σε λεμφώματα, μελανώματα και νεφρικούς καρκίνους. Στην συνέχεια έχει δοκιμαστεί μεγάλος αριθμός εμβολίων και ανοσοκυτταρικών θεραπειών όπου πάλι, παρά τις αρχικές προσδοκίες, τα αποτελέσματα ήταν απογοητευτικά. Σε αυτές τις μελέτες παρατηρηθκε ότι η ανάπτυξη ειδικών κλώνων που αναγνώριζαν καρκινικά αντιγόνα in vitro δεν ήταν επαρκής για μια επιτυχή ανοσοαπάντηση. Τελικά όμως η ανοσοθεραπεία του καρκίνου επανέρχεται στο προσκήνιο με ιδιάιτερη έμφαση, αφού τα τελευτάια χρόνια ανεδείχθησαν με μεγαλύτερη σαφήνεια μηχανισμοί ανοσοανοχής που μάλλον ήταν υπεύθυνη για τις αποτυχίες του παρελθόντος. Ετσι, μονοκλωνικά αντισώματα που αδρανοποιούν επιφανειακούς υποδοχείς που σχετίζονται με την ανοσοανοχή εισήλθαν με επιτυχία στην κλινική πράξη. Η ιπιλιμουμάμπη στρέφεται κατά του υποδοχέα CTLA4 των Τ-λεμφοκυττάρων και αναστέλλει την αδρανοποίηση μετά από επαφή με κύτταρα που παρουσιάζουν αντιγόνα. Ετσι τα Τ-λεμφοκύτταρα ενεργοποιούνται αποτελεσματικά μετά από παρουσίαση των καρκινικών αντιγόνων από μακροφάγα. Η ιπιλιμουμάμπη έχει έγκριση για την θεραπεία του μελανώματος. Μια άλλη πολύ σημαντική οδός αδρανοποίησης των Τ-λεμφοκυττάρων αφορά τον άξονα Programmed cell death-1 (PD-1) και τον συνδέτη PDL-1. Το PD-1 εκφράζεται στην επιφάνεια των ενεργοποιημένων κυτταροτοξικών Τ-λεμφοκυττάρων ενώ τα καρκινικά κύτταρα εκφράζοντας τον συνδέτη του κατορθώνουν να τα αδρανοποιούν και να αποφεύγουν έτσι την ανοσοεπιτήρηση. Μονοκλωνικά αντισώματα κατά του PD-1 έχουν ήδη εγκριθεί για χρήση κατά του μελανώματος, του καρκίνου του νεφρού και του πνεύμονος με καλά αποτελέσματα, ενώ ερευνάται η χρήση τους σε πλειάδα άλλων όγκων. Η ανακάλυψη αυτών των αναστολεών της ανοσοανοχής έχει προκαλέσει αναθεώρηση όλης της ανοσοογκολογίας και αναζωοπύρωση του ενδιαφέροντος για μια όλο και πιο αποτελεσματική ανοσολογική απάντηση στο πρόβλημα του καρκίνου.

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Personalized medicine and pharmacogenomics: Challenges and perspectives

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The establishment of personalized medicine concepts to increase precision, along with the advent of pharmacogenomics as new discipline in medicine and pharmacy provide an intense scientific stimulus toward advancing clinical practice in disease prognosis, diagnosis and drug delivery. Although the capabilities for pharmacogenomics and personalized medicine look very promising in healthcare, their practical clinical utility documentation and worldwide application is quite challenging. However, through the application of specialized nanotechnology-based theragnostics loaded with therapeutics and validated biomarkers or imaging signals, the improvement of outcomes for individual patients is facilitated in a cost-affordable way as well as in real-time. Moreover, the implementation of pharmacogenomics knowledge into the challenging approach of physiologically based pharmacokinetic modeling permits the individualized drug dosage scheme selection in the clinical setting. The latter, it inevitably enables pharmacotyping to improve drug prescription process and thus the practical clinical utility of personalized medicine decisions to empower routine healthcare. Complementary, by integrating and translating nanotechnology and genomics knowledge, personalized medicine undoubtedly increases productivity and creates improved profiles for specific populations and individual patients for prognosis, diagnosis and drug treatment, as well as monitoring across medical research and clinical care. Importantly, this can be accomplished by ensuring maximum safety and efficacy profiles for most, if not all, individuals.

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Μεταμόσχευση ηπατοκυττάρων

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Η μεταμόσχευση ηπατοκυττάρων αποτελεί μία εναλλακτική πρόταση ως προς την μεταμόσχευση ήπατος σε παιδιά με μεταβολικά νοσήματα του ήπατος, καθώς και για οξεία ή χρονία ηπατική ανεπάρκεια. Πλεονέκτημα της μεθόδου θεωρείται η δυνατότητα διατήρησης του ιθαγενούς ήπατος, το οποίο στην οξεία ηπατική ανεπάρκεια έχει την πιθανότητα να αναγεννηθεί, ενώ στα μεταβολικά νοσήματα του ήπατος, λειτουργεί ως δικλείδα ασφαλείας για την περίπτωση της απόρριψης των ηπατοκυττάρων και δίνει την δυνατότητα επανάληψης της θεραπείας . Επιπλέον, η μεταμόσχευση ηπατοκυττάρων είναι λιγότερο επεμβατική, έχει μικρότερο κόστος, παρουσιάζει λιγότερες επιπλοκές από τη μεταμόσχευση ήπατος και η δυνατότητα κρυοσυντήρησης των ηπατοκυττάρων τα καθιστά διαθέσιμα για μελλοντική χρήση στη θεραπεία της οξείας ηπατικής ανεπάρκειας.

Τα ηπατοκύτταρα προέρχονται από ηπατικά μοσχεύματα τα οποία δεν χρησιμοποιήθηκαν για μεταμόσχευση. Συνήθως πρόκειται για οριακά μοσχεύματα λόγω αυξημένης λιπώδους διήθησης ή μεγάλου χρόνου ψυχρής ισχαιμίας, από ασταθείς ή και από ασυστολικούς δότες, ή από τμήματα μοσχευμάτων που δεν χρησιμοποιήθηκαν μετά από διαχωρισμό (δεξιό – αριστερό ήπαρ ή τμήμα IV). Η ποιότητα των ηπατοκυττάρων που απομονώνονται από τα ανωτέρω μοσχεύματα δεν είναι καλή και απαιτείται βελτίωση των τεχνικών εμπλουτισμού και κρυοσυντήρησής τους. Οι μέθοδοι εμφύτευσης ευρίσκονται υπό έρευνα, καθώς η αρχική επιβίωση των ηπατοκυττάρων στον λήπτη δεν είναι ικανοποιητική. Η ανοσοκατασταλτική αγωγή δεν έχει πλήρως τεκμηριωθεί, αν και πιστεύεται ότι απαιτείται μικρότερη δοσολογία απ' ότι στη μεταμόσχευση ήπατος. Η συνολική επιβίωση των μεταμοσχευθέντων ηπατοκυττάρων δεν ξεπερνά τους 6-12 μήνες, χωρίς να έχει διευκρινισθεί αν η αιτία είναι η απόρριψη, η απόπτωση ή η νέκρωση με άλλο μηχανισμό. Το κύριο εμπόδιο για την κλινική εφαρμογή της μεθόδου είναι η έλλειψη ανθρώπινων ηπατοκυττάρων και αυτό οδηγεί την έρευνα στη μελέτη των στελεχιαίων κυττάρων, των κυτταρικών σειρών και των κυττάρων από ξενομοσχεύματα.

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Safety and efficacy of transarterial radioembolization in hepatic malignancies

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Iintroduction

Transarterial Radioembolization (RE) with Yttrium-90 (^{90}Y) is an alternative locoregional treatment for patients with unresectable, chemoresistant hepatic malignancies. It was first described in 1965 and since then the technique has been subjected to many improvements and also has expanded its applications.

Background

Radioembolization is a type of brachytherapy based on the administration of ^{90}Y-loaded microspheres in the hepatic arterial vasculature. Microspheres which contain ^{90}Y, a pure beta emitter, occlude small arterioles that feed tumors, resulting in tumor shrinkage, predominantly due to radioactivity and not ischemia. Indications for RE include disease not amenable to surgical resection, liver transplantation or ablative therapy or refractory to chemotherapeutic alternatives. Absolute contraindications include active hepatitis, life expectancy less than 3 months, unacceptable lung shunt and untreated portal hypertension. Relative contraindications generally include portal vein invasion (PVI), INR >1.5, GFR <35 ml/min and serum bilirubin >2 mg/dl whereas age is not a contraindication. Pre-treatment evaluation includes clinical status, blood tests and anatomic assessment with CT or MRI.

Safety

In general radioembolization is a well-tolerated and safe treatment. The post-radioembolization syndrome is less severe compared to other embolic therapies and may include fatigue, vomiting, nausea and abdominal pain, which can be treated with common antinauseants, antiemetics and strong analgesics. Also patients usually report fever, decreased appetite and lethargy after treatment. Major complications are rare and may include lung toxicity, lymphocytopenia, radiation-induced gastric ulcers, jaundice, cholecystitis, hepatic abscess, radiation hepatitis and liver failure. Most serious complication is radioembolization-induced liver disease (REILD) which is the result of excessive irradiation of healthy hepatic parenchyma.

When performed in elderly patients RE is as effective and as well tolerated as in younger patients. Furthermore it is safe to be performed on a remnant liver. Overall survival is similar when comparing patients with previous hepatectomy to non-hepatectomy patients. In addition RE provides concurrent treatment of ipsilateral hepatic tumors along with hypertrophy induction of the contralateral lobe, with a slower rate than that achieved by other methods.

Efficacy

Currently treatment with ^{90}Y is indicated as a palliative treatment for unresectable primary and metastatic liver tumors when treatment with chemotherapeutics has failed or the patient refuses chemotherapy treatment and other curative treatments are not indicated.

To date transarterial radioembolization has generally been reserved for patients with intermediate/advanced BCLC stage hepatocellular carcinoma (HCC) who are not candidates for transarterial chemoembolization due to PVI. Radioembolization has proved

clinical effectiveness in intermediate/ advanced hepatocellular carcinoma. Many studies reported that treatment with ^{90}Y show similar levels of effectiveness or even longer survival rates to transarterial chemoembolization in patients with intermediate HCC and also has a better tolerance profile. Also in some cohorts of patients with HCC and PVI invasion, RE was associated with a more prolonged survival to sorafenib.

Transarterial radioembolization is also being increasingly used for treatment of metastatic colorectal cancer (mCRC), especially in patients who have chemoresistant disease. When used as first line therapy, RE showed higher objective response rate in patients who underwent RE in addition to hepatic artery chemoinfusion of floxuridine compared to those who received chemoinfusion alone. Transarterial radioembolization has also been used with second or third-line chemotherapy, mostly with irinotecan or 5-FU or even as a palliative treatment in patients with chemorefractory disease. A recent systematic review revealed a median overall survival of 10-12 months, with 31% partial response and 41% stable disease. Furthermore other studies show that transarterial radioembolization has a favorable risk/benefit profile among patients who had previously received more than three lines of chemotherapy. However more trials with large series of patients are needed to identify the patients who benefit most from this modality.

Beyond HCC and mCRC, RE has been used to treat cholangiocarcinoma and metastatic disease to the liver from other primary tumors, such as breast cancer (BRCLM), lung cancer, pancreatic cancer, neuroendocrine tumors (NETs), renal cancer, ocular melanoma and others. Even though the indications for RE in these patients are not well defined, results of small studies are favorable.

Based on pooled analysis of data from twelve studies, the overall weighted median survival for patients with intrahepatic cholangiocarcinoma who underwent ^{90}Y radioembolization treatment was reported to be 15.5 months while seven patients were able to be downstaged to surgical resection. Treatment with 90Y also shows encouraging local response rates for BRCLM. Patients with repetitive lobar treatment or without prior angiosuppressive therapy had better outcomes whereas patients with high liver tumor burden had worse.

In general many studies also report effective and safe use of radioembolization for liver dominant disease in metastatic neuroendocrine tumors (mNETS). After RE there is a positive effect on symptoms, quality of life, response criteria, and survival in various stages of progression

Conclusion

Transarterial radioembolization is an emerging treatment modality and has to offer in patients with hepatic malignancies, especially when curative therapies such as surgery might still be an option. To date RE is predominantly performed in a palliative setting. However studies show that RE can result in downstaging patient to resect disease or be a candidate for a transplant and inducing contralateral lobe hypertrophy. Moreover RE may be advantageous in the treatment of patients with PVI.

Patient selection is very important as long as benefit to any given patient relies on tumor type and patient status. Recent data support the safety and efficacy of Y-90 radioembolization in various applications but still comparative studies are needed to fully define its role in oncology.

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Exposure to cosmic radiation

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We are continuously exposed to different types of natural and artificial sources of ionizing radiation. These sources include among others radon, medical (diagnostic and therapeutic) applications, consumer products, naturally occurring radionuclides, cosmic radiation, etc.

The cosmic radiation was discovered by the Austrian physicist Victor Hess in 1912. It consists of: a) high energy charged particles (galactic cosmic rays) that originate outside the solar system and b) solar energetic particles which are intense streams of high energy charged particles emitted from the Sun during solar flares and solar coronal mass ejections. Lower energy charged particles interact with the magnetic field of Earth and they are deflected back to space. However, high energy particles are slightly deflected and they can enter the Earth's atmosphere.

As cosmic radiation enters the atmosphere it interacts with atoms of air and produces more particles (protons, neutrons, etc.) in the form of a cascade. The flux of the particles continuously increases, reaching its max value at about 20km above the sea level. Below this level the intensity of the cosmic radiation decreases as a function of altitude due to continuous interactions and energy losses.

At sea level the cosmic radiation contributes about 10% of the total dose rate from natural radiation to which human beings have always been exposed; however, at higher altitudes and especially in outer space it is the dominant source of radiation[1]. Based on the energy and the type of the charged particles consisting cosmic radiation it can cause either stochastic or deterministic biological effects. As the intensity of the charged particle flux depends on the altitude, awareness regarding the doses received and the associated risk is important for the aircraft crew. The effective doses of the aircraft crew due to the cosmic radiation can be calculated directly as a function of geographic location, altitude and solar cycle phase taking in to account flight and staff roster information[2]. According to the analysis results of the data collected in the framework of the PRISMA project run by EEAE, the annual effective dose of the air crew of Greek airline companies is comparable to the respective doses of the personnel participating in medical diagnostic and therapeutic procedures with ionizing radiation.

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Cosmic Radiation and Immune System

P. Boura

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All living organisms on earth are subject to a hostile environmental factor, the natural radiation. The so-called natural radiation consists of cosmic radiation, terrestrial gamma rays, radionucleotides in food and inhaled isotopes of radon with their decay products. The distinctive effects of cosmic radiation on human health have been a challenge for the medical science, since this environmental factor penetrates earths' protecting atmosphere and cannot be isolated in any experiment conducted on earth. Space travelling has given the optimal opportunity to study such effects. The sterilized compartment of a space station, the absence of any other environmental factor and the enhanced presence of cosmic radiation, provide the proper field to study the effects of cosmic radiation on any form of life.

Space travel may alter physiological parameters not only via the effects of cosmic radiation, but also thru the augmented G forces the crew experiences during take-off and return to the planet. These combined aggravating parameters have been isolated by conducting the same experiments in short flight missions and in long space flights. In short flight the effects of burr acceleration forces are predominant, whereas in long flights, they contribute to a lesser extend to the experiments, and the results can be safely attributed to cosmic radiation.[1]

Different types of experiments have been conducted on the space travel program in order to estimate the cosmic radiation effect on the immune system. Two different types of studies have been conducted: 1. Observational studies on astronauts exposed to the spatial environment. In these studies, pre- and post-flight assessment of diverse parameters investigated the effects of cosmic radiation on the function of the immune system. 2. Prospective studies in human cell cultures and mice. These studies have given the opportunity to study interactions between cosmic radiation and specific functions of the immune response. Such studies indicated that in animal models, prolonged space flight travels result in a reduction of spleen and thymus volume accompanied by decreased lymphocyte counts. Cytokine profile is also altered and a reduction on IL-6 and IFN-γ levels is noticed. Intracellular signaling, including Nf-κβ pathway activity, is suppressed whereas non-canonical Nf-κβ signaling does not seem to be impaired.[2]

Several studies confirm that alterations on the immune function involve predominantly the innate immune system rather than the adaptive compartment.[3] The innate immune system primarily recognizes environmental antigens which could impose a threat to the organisms' homeostasis. The sterilized compartment of space stations gave the opportunity to observe whether innate immune system function can be altered not only following pathogen associated molecules (PAMPs) interactions, but also in the presence of non-microbial, danger associated signals (DAMPs). Cosmic radiation results in up-regulation of Heat shock Proteins (HSPs) and TLR4 expression. It is investigated whether these alterations are the result of deprivation of PAMPs' signals or are caused by the presence of diverse DAMPs, probably due to factors like increased oxidative stress in space.

It is expected that experiments in space environment will not only elucidate pathophysiological mechanisms of certain diseases, but they will also give rise to possible therapeutic options on earth.

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Διακυμάνσεις των ορμονών στο διάστημα (ENMF)

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ανοσία *2016; 12, 1: 52 – 53*

Ο άνθρωπος κατά τον Αριστοτέλη από την φύση του αναζητά την γνώση και δεν θα σταματήσει να ερευνά ποτέ, διότι η γνώση δεν έχει ούτε αρχή ούτε τέλος.

Βέβαια οι γνώσεις μας μέχρι τώρα για τον τομέα της Ενδοκρινολογίας στο Διάστημα είναι περιορισμένες και σε αυτό συντελούν:

1. Η πολυπλοκότητα του τομέα αυτού με την συνεχή αύξηση του αριθμού των ήδη υπαρχουσών ορμονών, των παραγόντων απελευθέρωσης και των προδρόμων ουσιών, καθώς και των αλληλεπιδράσεων μεταξύ τους, μέσω ποικίλων μηχανισμών.

2. Η δυσκολία διαχωρισμού των επιδράσεων της έλλειψης βαρύτητας από την επίδραση του στρες κατά την διάρκεια διαφόρων καταστάσεων, όπως από την εκτόξευση, την απομόνωση και τον περιορισμό κατά την διάρκεια της πτήσης, ως και κατά την διάρκεια επανεισόδου στην γήινη ατμόσφαιρα και της επαναπροσαρμογής στο γήινο περιβάλλον.

3. Οι περιορισμοί των πειραμάτων κατά την διάρκεια της πτήσης, ο μικρός αριθμός των πειραματοπροσώπων, ο περιορισμένος αριθμός δειγμάτων των ορμονών με παλμικές αυξομειώσεις όπως π.χ. η αυξητική ορμόνη.

4. Η ενόχληση που αισθάνονται οι αστροναύτες από τα αντιρροπιστικά μέτρα που λαμβάνονται για την προστασία τους στο Διάστημα

5. Η ανεπάρκεια δεδομένων μετά το τέλος των αποστολών για να συγκριθούν με τα αποτελέσματα εν πτήση.

6. Περιορισμένα συμπεράσματα τόσο από πειράματα σε ζώα όσο και από μελέτες σε άλλες συνθήκες προσομοίωσης του διαστήματος (π.χ. κλινοστατισμος με κλίση 6°.

Στον τομέας της Ενδοκρινολογίας στο διάστημα ερευνώνται διαδοχικά 9 άξονες:

1. Ο άξονας υποθαλάμου-υπόφυσης-επινεφριδίου, ο οποίος εμπλέκεται σε αντιδράσεις στρες και περιπλέκει περεταίρω την κατανόηση των αποτελεσμάτων μετά την επιστροφή από το διάστημα

2. Στον ίδιο άξονα οι παλμικές αυξομειώσεις των ορμονών δημιουργούν πρόβλημα για την λήψη αντιπροσωπευτικών τιμών (π.χ ωχρινοτρόπος ορμόνη). Η αναπαραγωγή στους επίμυες στο διάστημα είναι εφικτή, αλλά υπάρχει ανάγκη περισσοτέρων ερευνών και για το γυναικείο φύλλο, αλλά και για το ανδρικό διότι τα μέχρι τώρα δεδομένα δείχνουν αναστρέψιμη μεν, αλλά δυσλειτουργία των όρχεων στο διάστημα.

3. Ταχεία αποδόμηση των οστών στην αρχική φάση της πτήσης στο διάστημα, η οποία μπορεί να οδηγήσει σε καταστροφικές συνέπειες τους πρώτους 3 μήνες αλλά συνεχίζει η αποδόμηση των οστών και μετά τους 3 μήνες παραμονής στο Διάστημα αλλά με επιβραδυνόμενο ρυθμό.

4. Ο άξονας υποθαλάμου-υπόφυσης-ενδοκρινών αδένων περιλαμβάνει την προλακτίνη και την αυξητική ορμόνη. Η αυξητική ορμόνη ενεργεί επίσης ως ορμόνη του στρες και η έκκρισή της μειώθηκε δραματικά σε πειράματα σε ποντίκια κατά την διάρκεια της διαστημικής πτήσης.Δεν παρατηρήθηκε όμως το ίδιο και στους αστροναύτες. Η διαφορά αυτή μπορεί να οφείλεται σε διαφορετική ρύθμιση της έκκρισης της αυξητικής ορμόνης μεταξύ των ποντικών και των ανθρώπων.

5. Ο άξονας υποθαλάμου-υπόφυσης-θυρεοειδούς περιλαμβάνει τις ορμόνες του θυρεοειδούς θυροξίνη και τριιωδοθυρονίνη, που μειώνονται στο διάστημα, γεγονός που υποδηλώνει ήπιο υποθυρεοειδισμό.

6. Ο άξονας ρενίνης-αγγειοτενσίνης-αλδοστερόνης, ο οποίος ρυθμίζει τα υγρά και τους ηλεκτρολύτες,

και περιλαμβάνει την αντιδιουρητική ορμόνη και δύο νατριουρητικά πεπτίδια που έχουν επιδείξει παράδοξη συμπεριφορά στο διάστημα.

7. Η Ρύθμιση της μάζας των ερυθρών που περιλαμβάνει την ερυθροποιητίνη. Ακόμη δεν έχει πλήρως εξηγηθεί γιατί παρουσιάζεται η αναιμία στο διάστημα.

8. Το ενδοκρινικό πάγκρεας περιλαμβάνει την ινσουλίνη και γλυκαγόνο, με απώλεια της ευαισθησίας στην ινσουλίνη στο διάστημα λόγω έλλειψης άσκησης, φαινόμενο που απαιτεί περισσότερη μελέτη πριν από την μεγάλη παραμονή του ανθρώπου στο διάστημα.

9. Το συμπαθητικό σύστημα ενεργεί μέσω της επινεφρίνης, νορεπινεφρίνης και ντοπαμίνης και φαίνεται να έχει αυξημένη δραστηριότητα στο διάστημα, σε αντίθεση με ό, τι πιστευόταν ευρέως μέχρι τώρα.

Από τα ανωτέρω συμπεράσματα, είναι σαφές ότι απαιτούνται πολύ περισσότερες μελέτες σε όλους τους τομείς της Ενδοκρινολογίας. Η σημαντικότητα των ερευνών στο Διάστημα είναι ότι μελετώνται τα συστήματα του ανθρωπίνου οργανισμού όταν λείπει ο συντελεστής «βαρύτητα», βάσει της οποίας έχει προσαρμοστεί και εξελιχτεί το ανθρώπινο γένος εδώ και χιλιάδες χρόνια.

Οι έρευνες στο διάστημα θα μας δώσουν μια πληρέστερη κατανόηση των εσωτερικών μηχανισμών ομοιόστασης. Το σημαντικότερο σημείο είναι ότι οι αλλαγές που υφίστανται ορισμένα ενδοκρινικά συστήματα στο διάστημα είναι παρόμοιες με εκείνες που παρατηρούνται κατά τη γήρανση, αλλά και την καθιστική ζωή. Σημαντικό είναι ότι μετά το πέρας της διαστημικής πτήσης και κατά την επιστροφή του ανθρώπου στην Γη, ανακτώνται όλες οι φυσιολογικές λειτουργίες μέσα σε λίγες εβδομάδες ή και μήνες. Αυτό ισχύει ιδιαίτερα για τα συστήματα που ρυθμίζουν το μεταβολισμό των μυών και των οστών και την αναπαραγωγή, όπως ακριβώς συμβαίνει και με το ανοσοποιητικό, νευροαισθητηριακό, και το καρδιαγγειακό σύστημα. Περαιτέρω διαστημικές έρευνες μπορούν να μας βοηθήσουν να βρούμε νέες ιδέες στην παθοφυσιολογία της γήρανσης και της χρόνιας ακινησίας και ελπίζουμε στην ανάπτυξη νέων μηχανισμών πρόληψης των επιπλοκών από αυτές.

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The mutanome as a biomarker in the era of immune checkpoint inhibitors for cancer treatment

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Tumor cells use a great variety of immunosuppressive mechanisms to escape immune surveillance. This has prevented effective immunotherapy against tumors for decades. Recently immune checkpoint inhibitors targeting the CTLA-4 and PD-1 T cell co stimulatory pathways have been used with relative success for the treatment of various malignancies not responding to classical chemotherapeutic agents. These findings suggest that leverage of the anergic stimuli delivered by tumor cells to the surrounding immune cells can be overridden and an efficient immune response can be used for the treatment of malignancies. Today at least three immune check point MoAb have received FDA approval for clinical use and showed very promising results for the treatment of metastatic melanoma. However we are still lacking prediction biomarkers that can identify patients with a clear benefit from this type of therapies.

Recently NGS based methods have been proven extremely effective for the discovery of somatic mutations and the corresponding RNA expression in tumor cells. This prompted several research groups to focus attention to a new type of promising biomarkers that are neo antigens (or neo epitopes) expressed by tumor cells. Indeed these neo antigens result from tumor specific somatic mutations and are characteristic of each tumor and each patient (also called the mutanome). They are probably «seen» as non self antigens by the immune system leading to potent immune responses when an immune check point inhibitor is used as an immune system stimulant. More recently several studies have shown that the quantity and the quality of these neo antigens are predictive of the clinical benefit of patients. The role of neo antigen load and cytolytic signatures seem to be one of the most promising biomarkers of response of immune checkpoint inhibitors in a new era of anti cancer treatment..

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Neutrophil extracellular traps (NETs): An emerging immune mechanism in inflammatory diseases

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Neutrophils have a key role in innate immunity and are the first cells recruited in vast numbers to the site of inflammation. Neutrophils encounter and kill microbes intracellularly upon phagocytosis. Furthermore, they degranulate lytic enzymes that destroy pathogens. In 2004, Zychlinsky and his colleagues reported another aspect of neutrophil microbicidal activity, the release of Neutrophil Extracellular Traps (NETs) that captures and kills extracellular microbes[1].

NETs consist of extracellular chromatin fibres decorated with various neutrophil-derived granular, cytoplasmic and nuclear proteins[1,2]. NETs are formed after phagocytosis of pathogens or in response to inflammatory agents and cytokines, such as LPS, G-CSF, C5α, IL-8, TNF, IFNγ and IFNα. Additionally, immunocomplexes and activated platelets have been shown to trigger NET formation[2-4]. It has demonstrated that NET formation is a well-regulated process that requires reactive oxygen species (ROS) generation and the synergistic effect of neutrophil serine proteases elastase and myeloperoxidase[5,6]. Importantly, autophagy has been also reported to be required for the induction of NETosis[6,7].

NET-mediated cell death (NETosis) is morphologically distinct from other classical cell death processes, like apoptosis and necrosis, given that it is characterized by the disruption of the nuclear membrane, chromatin decondensation, and the mixing of nuclear contents with cytoplasmic and granular proteins, and finally, the release of NETs[8].

Currently, a great body of evidence have highlighted the fundamental role of NETs in the pathogenesis of numerous neutrophil-mediated inflammatory disorders and their consequences including systemic autoimmunity, vascular disease, thrombosis and fibrosis[2,4,9-15]. The fact that neutrophil inflammatory enzymes (e.g. elastase, myeloperoxidase) are localized on NETs in non-infectious diseases, suggest that these structures may amplify the inflammatory responses of these disorders. Additionally, NETs can expose a range of specific autoantigens and may induce the production of autoantibodies[13,14]. Indeed, proteins externalized in the NETs could undergo posttranslational modifications such as acetylation, methylation and citrullination, and/or proteolytic cleavage making NETs an important source of neoantigens, which circumvent immune tolerance and activate autoimmune responses in predisposed individuals. Thus, besides their beneficial antimicrobial function, excessive formation of NETs or ineffective clearance can lead to tissue damage as a result of aberrant inflammatory response[2].

Of note, several research groups, including our own, have demonstrated that "*all NETs are not equal*". This implies that NETs produced in the context of different disease entities are qualitatively different and express disease-specific proteins. For example, IL-Iβ has been found on NETs associated with autoinflammation in familial Mediterranean fever[12], autoantigens on NETs have been associated with autoimmune diseases, such as rheumatoid arthritis[13] and systemic lupus erythematosus[14], tissue factor on NETs has demonstrated to promote thrombosis occurring in the context of sepsis[10], ANCA-vasculitis[15] or acute coronary syndrome[4], while in other models, NET-bound IL-17

has been linked with a fibrotic response[11]. Moreover, the integrity of NET chromatin scaffold is crucial constituting the vehicle for biologically active proteins, specifically produced or acquired, and stored in the cytoplasm of neutrophils[2,4,11].

Taken together, the development of new diagnostic tools based on the qualitative and quantitative detection of disease-specific NET proteins in biological material will facilitate early and accurate diagnosis/discrimination of various neutrophil-mediated inflammatory diseases, greatly needed in everyday clinical practice. Moreover, unraveling the triggers and mechanism of NET formation mechanism implicated in the pathophysiology of these disorders and analyzing the mechanism-of-action of "anti-NETotic" agents will provide novel and safer targets for therapeutic intervention.

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Critical analysis of therapeutic algorithms in Rheumatoid Arthritis: A pharmacoeconomical approach

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Rheumatoid Arthritis is the most common systemic autoimmune disease, affecting almost 1% of the global population. Novel biological therapies have been very effective in controlling the disease and are widely adopted in therapeutic algorithms, in some cases even as first-line treatment regiments.

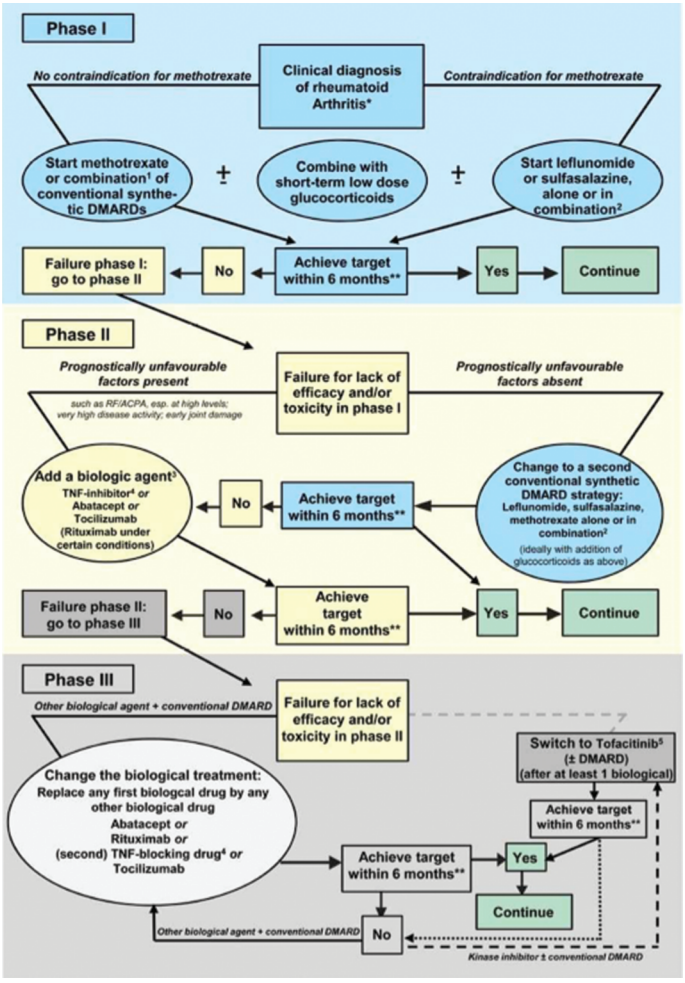
Nevertheless their outstanding performance, biological agents are much more expensive than conventional Disease Modifying Anti-Rheumatic Drug (cDMARD) therapy. In an era of global economic crisis that in some countries as Greece has led to persistent austerity for the last 6 years, a revaluation of the therapeutic approach for rheumatoid arthritis based on pharmacoeconomics is mandatory.

According to recent data, RA is an expensive disease. Statistical reports in the United States of America indicate that RA absorbs 0,3% of the gross national product and that direct medical expenses for each patient may rise up to almost 6.000$ per year. Indirect costs (due to incapability and loss of productivity) are 3-4 times higher. If on these expenses is added the cost of biological therapies, then a patient may need more than 20.000$ per year for medical and pharmaceutical support.

Therapeutic regiments for the treatment of RA include conventional (cDMARDs) and biological (bDMARDs) agents. Until the biological era, patients were treated with cDMARD monotherapy or combination therapy. 30% of these patients would not retain sustained remission and would need pulse treatment with iv corticosteroids or even alkylating agents (cyclophosphamide). Biologics have revolutionized the treatment of these patients, achieving in a short time prolonged disease remission, sparing them from the aggravating side effects of cosrticosteroid and alkylating iv therapies.

On 2013, EULAR (European League Against Rheumatism), the European Rheumatologists' society, issued guidelines for the treatment of RA (picture 1). According to these guidelines, initial therapy of RA should consist of a monotherapy or combination cDMARD therapy. Failure or intolerance of this therapy are prerequisites for the initiation of a biological agent. EULAR refers to cDMARDs for the agents methotrexate (MTX), sulfasalazine (SASP) and leflunomide (LEF). cDMARDs as cyclosporine-A (CyA) and azathioprine (AZA) are not included in the EULAR guidelines, impoverishing the cDMARD therapeutic choices, leading to premature initiation of bDMARDs.[1,2]

Published data supports that the agents excluded from the EULARs' list of cDMARDs (CyA and AZA) perform equally to MTX in controlling RA. A 10-year follow up study of CyA administration, indicated that 30% of the patients who receive CyA monotherapy as first cDMARD, remain on this regiment for more than 10 years. The investigators have established a step-up combination therapy for non-responders with AZA, an approach that was found to be particularly successful, recording low toxicity and high tolerability.[3] Such studies indicate that the cDMARDs armature is a more extended family of agents than those described by the 2013 EULAR guidelines and implication of these agents in therapeutic RA algorithms may sus-



Picture I. *EULARs' 2013 therapeutic algorithm for RA.*

tain prolonged remission, sparing the patients from much more expensive biologic agents.

Another issue regarding pharmacoeconomic parameters of biological agents must be taken into consideration. Some of the bDMARDs exist in both iv and subcutaneous (sc) forms. Both have proven to be equally effective. Nevertheless, upon application, iv administration requires a periodical hospitalization in the infusions department, augmenting the cost of the applied therapy, a cost that can be avoided by applying the sc form of the agent.

Current therapeutic protocols include almost 10 clinically applied bDMARDs. On an era of economic crisis, bDMARDs administration should be cost/effective for each patient, taking into account pharmacoeconomical studies and keeping in mind the effectiveness of cDMARDs combination therapy.

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Digital Capillaroscopy in current medical practice: cost-beneficial analysis

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ABSTRACT

Nailfold capillaroscopy is a highly sensitive, inexpensive, simple, safe, and noninvasive imaging technique used in the morphological analysis of nourishing capillaries in the nailfold area. The idea of capillaroscopic evaluation "started" from the observations of the scientists of 18th century. Today, with the assistance of digital video nailfold capillaroscopy (NVC), we can evaluate in details the architecture of microvasculature and search for signs of vasculopathy. Typically, early stages of fibrotic vasculopathy characterized by the presence of microhemorrhages with normal number of capillaries per visual field (>9/mm2), whereas progressed sclerosis produce the formation of new giant vessels, ramifications and reduced density of the vascular network (late scleroderma pattern). Whereas specific capillaroscopic findings have already included in EULAR (2013) criteria for early diagnosis of Systemic Sclerosis (SS), new studies investigate the role of NVC in monitoring the course of the SS and its value in other rheumatic and non-immune diseases as well.

Key words: capillaroscopy, Systemic Sclerosis.

Capillaroscopic examination consist a necessary tool for the investigation of Raynaud's phenomenon (RP) since it is well known that in primary RP there is functional impairment due to excess vasoconstriction but no anatomical changes are observed. Well defined capillaroscopic findings have been described in various stages of fibrotic vasculopathy although overlap with other rheumatic diseases has been reported. Abnormalities in capillary network have been suggested as an additional criterion for the preliminary classification of systemic sclerosis (SS) and are included in the new EULAR diagnostic criteria for the diagnosis of SS.[1,2,3,4]

Recent studies investigate the prognostic value of capillaroscopy findings for the development of new digital ulcers in patients with SS and/or the correlation of microvascular appearance with other manifestations of the disease such pulmonary hypertension and interstitial pulmonary fibrosis. In Clinical Immunology unit of the 2nd Internal Medicine Department we studied the presence of autoantibodies [autoantibodies against topoisomerase I (SCL-70) and III (anticentromere)] and the internal organ involvement in SS patients in correlation to the pattern of capillaroscopic images, and we found that the late scleroderma capillaroscopic pattern is correlated with the positive autoantibodies in serum and more severe disease.[5,6,7]

Other studies evaluate potential biomarkers in correlation to various capillaroscopic parameters. As an example, urinary concentration of 8-isoprostaglandin F2a, a marker of oxidative stress and in SS patients, correlates with peripheral microangiopathy, particularly in patients with active and late capillaroscopic patterns. Finally new evidence suggests that capillaroscopy can be used for monitoring the drug-induced modifications of microvessels. Most research into the changes in microvascular morphology observed with capillaroscopy has so far focused on bosentan treatment. ET-I receptor blockade may favorably influence the structural vascular abnormalities, but the results are controversial.[8,9]

A growing interest exists on the exploitation of capillaroscopy in other medical fields, besides rheumatic diseases. New studies correlate the microvascular abnormalities observed by capillaroscopy to non-

immune diseases that is known to affect small vessels like arterial hypertension and diabetes mellitus. The enormous impact of NVC in Rheumatology are discussed and new prospects in various disciplines of internal medicine are explored.

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ΑΝΑΡΤΗΜΕΝΕΣ ΑΝΑΚΟΙΝΩΣΕΙΣ (E-POSTERS)

ΕΡΕΥΝΗΤΙΚΕΣ ΕΡΓΑΣΙΕΣ

1

PHYSICIAN BURN-OUT IN GREEK INTENSIVE CARE UNITS: A QUALITATIVE ANALYSIS OF ASSOCIATED PARAMETERS

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INTRODUCTION: Emotional burn-out is a common phenomenon among physicians working in intensive care units (ICUs); However there is yet no agreement as to which specific circumstances pose the most important emotional burden. This study aimed to investigate which of the factors related to decision-making or the ICU overall functioning are associated with physician burn-out.

MATERIAL-METHODS: The study used a cross-sectional design. Data were collected via anonymized self-completed questionnaires which had been e-mailed to several ICUs throughout Greece. Maslach Burn Out Inventory was used to diagnose burn-out, while the State Trait Anxiety Inventory (STAI) was utilized to evaluate level of stress. Group comparisons were conducted using the Student's t-test for continuous or the Chi-square test for qualitative variables. Level of $p<0.05$ was considered statistically significant.

RESULTS: 82 questionnaires were collected from 17 ICUs (response rate: 70.8%) From the responders, 40.2% presented with burn-out. These were more often male (56.3 vs. 31.9%; $p=0.031$), with higher STAI score (93.9±14.8 vs 81.6±13.7; $p<0.001$) than the rest. Age (45±8 vs. 45.8±8.3), marital status and working hours were similar between the groups. Physicians with burn out reported a significantly higher emotional burden due to the need to rush into quick decisions ($p=0.004$), to act accurately ($p=0.044$), to cope with unpredictable situations ($p=0.002$), to communicate with patient's relatives ($p=0.024$) and to face patient's death ($p=0.003$), while they were more afraid of conducting a medical error ($p=0.002$).

CONCLUSION: Physician burn-out is a common phenomenon in Greek ICUs and is associated with several factors related to decision-making.

2

SERUM CGRP LEVELS COULD BE USED AS A SIGNAL BIOMARKER SUGGESTING THE INCIDENCE OF TWO DISORDERS UNLIKELY TO OCCUR CONCURRENTLY: ALZHEIMER'S DISEASE VERSUS BREAST CANCER

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AIM: To assess the contribution of serum calcitonin gene-related peptide (CGRP) variation in distinguishing two diseases that appear implausible to occur concurrently: breast cancer (BC) and Alzheimer's disease (AD); pathophysiologically interlinked at the ends of a spectrum.

PATIENTS AND METHODS: We used radioimmunoassay (RIA) to determine serum CGRP concentrations, which were subsequently compared (t-test) between patients with AD (n=17) and BC of different histological

subtypes [invasive ductal carcinoma (IDC) n=7, mixed IDC+DC in situ (IDC+DCIS) n=5 and DCIS n=5)]. Serum CGRP levels of AD and BC patients were compared to the corresponding of healthy controls (n=10).

RESULTS: Serum CGRP concentrations in AD, BC, and controls were (mean±SD: pg/mL): 179.7±50.4, 438.3±448.1, and 90.2±32.1, respectively. Significantly higher CGRP levels were revealed by t-test in BC as compared to AD patients (P=0.04) and controls (P=0.09). As compared to AD patients significant difference was determined only in mixed DCIS+IDC lesions of BC patients (P=0.00013). Patients with AD presented significantly higher CGRP levels as compared to controls (P=0.001). Non-significant difference was established between AD vs IDC (P=0.16) and AD vs DCIS (P=0.8).

CONCLUSION: Downregulation of CGRP expression seems to exhibit a critical role in AD progression, whereas a distinct correlation exists between CGRP upregulation and mixed DCIS+IDC. CGRP multilevel activity range suggests that the underlying pathophysiological mechanisms probably involve β-amyloid formation and deposition at lower levels in AD versus hypoxia-induced angiogenesis at high levels in BC. Our findings propound further research, potentially inducing a major clinical impact in terms of diagnosis and anti-CGRP-peptide treatment of both disorders.

3

CORRELATION BETWEEN SERUM CGRP OVEREXPRESSION AND MAMMOGRAPHIC BREAST DENSITY AS WELL AS CELL PROLIFERATION INDEX KI67 IN PATIENTS WITH MIXED IN SITU AND INVASIVE DUCTAL BREAST CARCINOMA (DCIS+IDC)

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AIM: To evaluate the variation of serum calcitonin gene-related peptide (CGRP) in patients with benign and malignant breast diseases. The possible correlation between this neuropeptide and mammographic breast density (BD%) as well as Ki67 is investigated.

SUBJECTS AND METHODS: We studied forty eight women with histologically confirmed breast diseases: mild epithelial hyperplasia (MEH): n=12, florid epithelial hyperplasia (FEH): n=5, atypical hyperplasia (AH): n=4, DCIS: n=5, DCIS+IDC: n=9 and pure IDC: n=13. RIA method was used to determine serum CGRP levels, which were subsequently compared (Mann-Whitney test) between the various groups. Computer-assisted methods were applied to calculate mammographic BD%, which was then correlated (linear regression analysis) with serum CGRP concentration. In twenty three women with histologically confirmed breast cancer (DCIS: n=6, mixed DCIS+IDC: n=8 and pure IDC: n=9), serum CGRP levels were compared (t-test) among the three groups and correlated (linear regression analysis) with Ki67 expression, which was immunohistochemically determined in the surgical specimens.

RESULTS: Significantly higher serum CGRP levels were revealed in DCIS+IDC lesions (versus: MEH P<0.001, FEH p<0.001, AH P<0.001, DCIS P<0.001 and IDC P<0.001). A statistically significant correlation was found between serum CGRP concentrations and BD% (r=0.947, P<0.0001).

In the group of patients with Ki67 determination, serum CGRP and Ki67 presented significantly higher values in mixed DCIS+IDC as compared to pure IDC (P=0.003 and P=0.04, respectively). A significant coefficient of correlation between Ki67 and CGRP was established by linear regression analysis (r=0.829, P<0.001).

CONCLUSION: Significantly increased serum CGRP levels were found in women with DCIS+IDC lesions. The significant correlation between serum CGRP levels and BD% as well as Ki67, augments the postulation that DCIS+IDC represents a distinct pathological entity and propounds a potential hypoxia-induced mitogenic role of CGRP. Our results introduce serum CGRP determination as a potentially useful, simple preoperative index regarding the nature or type of suspicious mammographic lesions, eventually guiding therapeutic decisions and adjunctive therapeutic administration of anti-CGRP peptides.

4

^{99m}TC-PYP MYOCARDIAL SCINTIGRAPHY: A SINE-QUA-NON IN DEPICTING TRANSTHYRETIN-RELATED CARDIAC AMYLOIDOSIS?

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OBJECTIVE: Cardiac amyloidosis (CA) constitutes a cause of cardiac insufficiency attributed to extracellular deposition of fibrillary proteins upon at least two different pathophysiologic backgrounds, with different clinical course and treatment. In light-chain cardiac amyloidosis (immunoglobulin light-chain amyloidosis-AL) the fibrils consist of light-chain immunoglobulins produced by a clonal plasma cell population in bone marrow. In CA related to transthyretin (transthyretin-related amyloidosis –ATTR), whether familial amyloid cardiomyopathy or senile systemic amyloidosis, misfolded monomers or dimers of the normally tetrameric protein of transthyretin are deposited in the myocardium. In this pilot study technetium-99m pyrophosphate (^{99m}Tc-PYP) was applied in order to prove its efficacy in terms of definitive ATTR diagnosis.

SUBJECTS AND METHODS: Technetium-99m-pyrophosphate (^{99m}Tc-PYP) was administered to sixteen patients (10 males, aged [mean±SD] 71±13y; 6 females, aged 64±8y) patients suffering from CA, aiming to discriminate scintigraphically between AL and ATTR. Diagnosis was confirmed by biopsy combined with the clinical and laboratory evaluation of the patients. Myocardial scintigraphy (planar and tomographic imaging) was conducted at 1, 2 and/or 3h after iv injection of 555-925MBq ^{99m}Tc-PYP. Myocardial radiotracer uptake was evaluated optically and semi-quantitatively, by drawing two regions of interest (ROI): one over the heart and another one over the contralateral hemithorax, to calculate the corresponding heart-to-contralateral (H/CL) count ratio. A cut-off H/CL value of 1.5 best discriminates between the two conditions, based on current international literature.

RESULTS: ^{99m}Tc-PYP scintigraphy revealed diffuse intense myocardial uptake upon visual evaluation that was also verified semi-quantitatively in 7 patients, all of which had ATTR. Faint or no myocardial tracer uptake was found in 4 patients diagnosed with AL. Five AL patients with a borderline positive scan on visual evaluation, showed an H/CL ratio below 1.5. The sensitivity and specificity of scintigraphy with ^{99m}Tc-PYP reached 100% in this small sample of patients.

CONCLUSION: Our results indicate that ^{99m}Tc-PYP scintigraphy, a simple, non-invasive and widely available method may prove a sine-qua-non in the identification of patients with the ATTR subtype. Thus, the proper treatment may be applied, avoiding endomyocardial biopsy in conjunction with immunohistochemical parameters or ultimately mass spectroscopy.

5

MOSFET TRANSISTOR DOSIMETRY OF THERMAL AND EPITHERMAL NEUTRON BEAMS FOR BORON NEUTRON CAPTURE THERAPY

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Boron neutron capture therapy (BNCT) is a two component or binary treatment modality that injects pharmaceuticals to localize tumor-targeting boron compounds ^{10}B to neoplastic cells. The region is then irradiated with low energy to epithermal neutrons and the stable isotope boron-10 (^{10}B) leads to primary

fission products that are a- particles and recoiling ^{7}Li sustaining a lethal $^{10}B(n,a)^{7}Li$ capture reaction. These have very short ranges similar to the dimensions of a biological cell and therefore the technique could achieve a high specificity that would spare normal cells and destroy all malignant ones to cure brain tumors, peripheral and intracranial metastatic melanomas and glioblastoma tumors. In order to achieve high LET radiation capable of preferentially accumulation in the cancerous cells destroying DNA, RNA and proteins in active molecules, low-energy to epithermal ($0.01*10^{-6}$MeV – 5MeV) neutron beams are used. To determine the dosimetric properties of near-threshold neutron beams of MOSFET, a systematic based on Monte Carlo N-Particle (MCNP) radiation transport computer program for simulations was used. The basic MCNP geometry for a SiO_2 thickness of 1μm is given in Fig.1 where all objects have cylindrical geometry. In the actual MOSFET, as the one manufactured by ukrainian company INR, SiO_2 is about 1μm thick and several 10s of μm in length and width. The Lithium target was included in the model with dimensions on the order of 1.8 mm while all other dimensions were invariant. The Metal Oxide Semiconductor Field Effect Transistor (MOSFET) shown in Fig.1 was designed using MCNP Visual Editor Version 19L and change its operational characteristics according to neutron irradiation exposed in mixed photon and electron fields. The MOSFET structural model presented were set up in an MCNP input file. The packaging (shell No.4) is made of an alloy known as KOVAR consists of Iron (Fe), Cobalt (Co) and Nikel (Ni). The kovar base inside the cap and leads were covered in Gold (Au).

The space inside the kovar base (shell No.1) is covered with glass consisted of cylindrical geometry with height 0.23 cm and radius 0.192 cm benchmarked for principle axes (X,Y,Z)=(0,0,0). The chip of silicon (shell No.3) consists of pure silicon is the yellow rectangle over the kovar base (Fig. 1) with length 0.06 cm, height 0.03 cm and volume of 0.06 cm thick. Shell No.8 was designed as the purple cylinder with radius 0.232 cm, height 0.5 cm and centre (0,0,0.135) consists of Iron (Fe), Cobalt (Co) and Nikel (Ni). Shell No.6 represents the Gate of transistor with green colour and cylindrical geometry of height 0.856 cm, radius 0.02 cm and centre (0.15,0,0). The silicon oxide layer (shell No.2) consists of SiO_2 and Al, designed as a dark blue rectangle in Fig. 1 with length 0.06 cm, height 0.001 mm and volume of 0.06 cm thick. This layer is not inherently sensitive to neutron response so the incorporation of encapsulating induces secondary photons and electrons that change threshold voltage in the silicon and the package. These particles are produced from interactions among neutrons within the packaging and contribute mainly on neutron response of the device. The Lithium Fluoride epoxy shield is presented in this model (shell No.13) consisting of Lithium (Li), Carbon (C), Hydrogen (H), Oxygen (O) και Fluorine (F) and cylindrical geometry of height 0.455 cm, radius 0.475 cm and centre (0,0,0.6125). The threshold voltage change depends on the ionisation of shell No.2 and the group of electrons and holes that stay trapped in this layer after the irradiation. Instead of executing a number of experiments with diverse monoenergetic sources of neutrons for every simulation it was determined to separate the spectral range into sampled uniformly discrete groups of energy beams of finite width. The neutron yields predicted by this program have been experimentally benchmarked for lithium (Table I) and non lithium epoxy encapsulation (Table II).

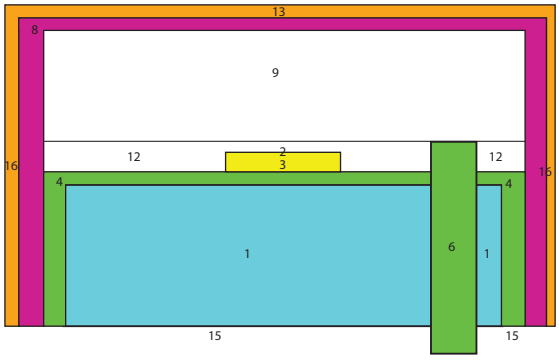

Figure 1. Geometry of MCNP model used for BCNT studies.

Table I. *A comparison of photon and electtron yields for thick lithium target.*

	Energy Beams			
Energy beams	Low Threshold (MeV)	Upper threshold (MeV)	Photon Yield	Electron Yield
1	0.01e-6	0.05e-6	4.0366e-11	2.7147e-6
2	0.05e-6	0.1e-6	5.3183e-11	2.7384e-6
3	0.1e-6	0.5e-6	1.4270e-10	7.9254e-6
4	0.5e-6	1e-6	1.8002e-10	1.0424e-5
5	1e-6	5e-6	5.5171e-10	3.8629e-5
6	5e-6	10e-6	5.5130e-10	3.0351e-5
7	10e-6	50e-6	4.0167e-10	1.0159e-5
8	50e-6	100e-6	6.1106e-10	1.4716e-5
9	100e-6	500e-6	3.6650e-10	2.6506e-5
10	500e-6	0.001	6.5299e-11	4.4986e-6
11	0.001	0.005	4.4071e-11	2.4797e-6
12	0.005	0.01	3.0762e-11	2.0774e-6
13	0.01	0.05	6.6227e-11	1.2283e-6
14	0.05	0.1	1.0917e-11	8.2790e-7
15	0.1	0.5	1.2738e-10	1.5645e-6
16	0.5	1.0	2.2124e-10	1.2530e-6
17	1	5	5.4725e-10	1.1205e-5

Table II. *A comparison of photon and electtron yields without lithium target.*

	Energy Beams			
Energy beams	Low Threshold (MeV)	Upper threshold (MeV)	Photon Yield	Electron Yield
1	0.01e-6	0.05e-6	2.9513e-9	1.7510e-4
2	0.05e-6	0.1e-6	2.1815e-9	1.2175e-4
3	0.1e-6	0.5e-6	1.1378e-9	6.9072e-5
4	0.5e-6	1e-6	4.6531e-10	4.1832e-5
5	1e-6	5e-6	1.3138e-9	8.5600e-5
6	5e-6	10e-6	5.8096e-10	3.4851e-5
7	10e-6	50e-6	1.3877e-10	8.6079e-6
8	50e-6	100e-6	5.7674e-10	1.6391e-5
9	100e-6	500e-6	3.4189e-10	2.4624e-5
10	500e-6	0.001	7.2719e-11	2.0265e-6
11	0.001	0.005	4.3887e-11	1.1438e-6
12	0.005	0.01	2.2693e-11	1.2249e-6
13	0.01	0.05	1.5613e-11	5.6402e-7
14	0.05	0.1	3.5220e-11	4.5101e-7
15	0.1	0.5	6.6399e-12	1.9150e-7
16	0.5	1.0	1.8521e-12	1.3664e-7
17	1	5	5.4725e-10	1.1208e-5

6

THE ROLE OF SERUM OSTEOPROTEGERIN IN METASTATIC PROSTATE CANCER

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INTRODUCTION: Prostate cancer is one of the most common malignant neoplastic diseases in men. Early control of the disease progression contributes significantly to survival rates and patients' life quality. On the other hand, osteoprotegerin is a dimeric glycoprotein, which affects bone metabolism and inhibits osteoclastogenesis. In the present study we evaluated the expression of osteoprotegerin in the serum of prostate cancer patients with or without skeletal metastases.

METHODS: The expression of serum osteoprotegerin, as measured by ELISA, has been studied in 82 patients with locally controlled prostate cancer, in 49 patients with bone metastatic disease and in a control group of 41 healthy males. At sampling time 65/131 of included patients were newly diagnosed, while 66/131 patients were already under hormonal therapy. All eligible prostate cancer patients had histologically confirmed malignancy. Serum total PSA was determined by an IRMA assay. We investigated the expression of osteoprotegerin in hormone-dependent and hormone-refractory prostate cancer and its relation with disease progression.

RESULTS: Among 131 patients with prostate cancer higher osteoprotegerin and PSA concentrations have been observed in bone metastatic patients' sera ($p<0.001$), while ROC analysis between the metastatic and locally controlled prostate cancer patients has shown a statistically significant area curve ($p<0.001$) and a cut-off limit of 89.6 pg/ml. Moreover, 15.3% of patients became hormone-resistant, with OPG values significantly increased compared with hormone-sensitive PCa ($p<0.001$).

CONCLUSIONS: It seems that, elevated levels of serum osteoprotegerin in patients with prostate cancer reflect bone metastatic extent and may potentially be used in metastatic patients' follow-ups.

7

ASSOCIATIONS OF NAILFOLD VIDEOCAPILLAROSCOPIC PATTERNS WITH AUTOANTIBODIES IN PATIENTS WITH SYSTEMIC SCLEROSIS: EXPERIENCE FROM A SINGLE CENTRE

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INTRODUCTION: Nailfold videocapillaroscopy (NVC) is a novel, simple, non-invasive method of examining microcirculation, playing an increasingly important role for evaluation and follow up of patients with Systemic Scleroderma (SS) and Raynaud's phenomenon (RP). Even though NVC findings are included in the latest 2013 EULAR diagnostic criteria, few studies have investigated the relation between NVC evaluation and immunological profile of SS patients. Purpose of the current research is the correlation of NVC patterns with the presence of autoantibodies in SS patients.

PATIENTS AND METHODS: 22 patients diagnosed with SS (EULAR 2013), were examined by two physicians experienced in NVC and autoantibodies against topoisomerase I (SCL-70) and III (anticentromere) were assessed.

RESULTS: From the 22 patients, 11 had early NVC patterns from which 7 had positive autoantibodies. Active NVC patterns were found in 7 patients with 5 having positive autoantibodies. Finally, all 4 patients with late patterns had positive autoantibodies. The results of the study imply that the positive autoantibodies and the internal organ involvement (denoted by interstitial lung disease-ILD) are found in higher percentage of patients as the fibrotic vasculopathy progresses.

Pattern		**Autoantibodies (+)**		**Autoantibodies (-)**	
Number of pts		Mean disease duration		Patients with ILD	
Number of pts		Mean disease duration		Patients with ILD	
Early	7/22	1 year 2/7	4/22	1 year	0/4
Active	5/22	3 years 2/5	2/22	3 years	1/2
Late	4/22	8 years 3/4	0/22		

CONCLUSION: It is indicated that vascular changes precede autoantibody presence. Therefore, it is important that new studies investigate the role of autoantibodies in pathophysiology of SS.

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8

TRANSCRANIAL DIRECT CURRENT STIMULATION. A PROMISING REHABILITATION METHOD FOR PATIENTS AFTER STROKE

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INTRODUCTION: Transcranial direct current stimulation (t-DCS) is a promising rehabilitation method to improve motor and cognitive deficits for patients after stroke by promoting neuronal plasticity. Studies combining functional neuroimaging with t-DCS have begun to define the local and distant effect of neuromodulation. Its neuromodulatory effects have been broadly attributed to long term potentiation and long term depression like mechanisms of synaptic plasticity. t-DCS protocols utilize two surface electrodes, one as the anode and the other as the cathode. The position of the electrodes appears to be critical for the distribution and direction of the current flow which may determine the effectiveness of the stimulation[1]. Neuroplasticity after a stroke might not always facilitate recovery. It is scientifically proven that plasticity may have maladaptive consequences. Abnormal activation patterns that have been seen in brain imaging studies may indicate this maladaptation[2].

The commonest model to explain the recovery of function after a stroke is that of inter-hemispheric imbalance. Many imaging studies suggest that after a stroke there is increased activity within the primary motor cortex of the contralesional hemisphere when the patient moves their stroke-affected hand. This increased activation is greater in patients who make a poor functional recovery and it decreases over time with functional recovery. Patients with better recovery show less activation in this region[3].

A study of chronic stroke patients with poor outcome revealed that they had increased inhibition from the contralesional MI position to the ipsilesional MIposition. These findings have raised the hypothesis that increased activity in the contralesional hemisphere is maladaptive to recovery[4].

Two major targets for neuromodulation exist in stroke rehabilitation:

1. directly increase of activity within the ipsilesional motor cortex (MIIpsi)

2. decrease of activity within the contralesional MI and indirectly increase of activity within the ipsilesional MI position.

A "bihemispheric montage" with the anode placed on MIIpsi and the cathode over MICont, could be promising[5].

MATERIAL AND METHODS: We performed a study in our stroke unit to investigate safety and efficacy of anodal t-DCS on the affected hemisphere in non-acute stroke patients. Eighteen (18) non-acute stroke patients (n=18,10 males- 8 females) aged between 60-80 years, received fifteen (15) sessions with anodal t-DCS (2mA for 20 min) to the ipsilesional MIposition and cathodal to contralesional MI position. Twenty (20) non-acute stroke patient (n=20, 11 males- 9 females) aged between 60-80 years, received sham stimulation and were the control group of the study. Motor ability and cognition were evaluated with FIM scale, Motricity index scale and the MMSE.

RESULTS: The majority of the patients had improvement of the clinical outcome in both motor ability and cognition. The patients that followed the procedure reduced the hospitalization days at the rehabilitation center ($p<0.01$). No side effects were detected during t-DCS application.

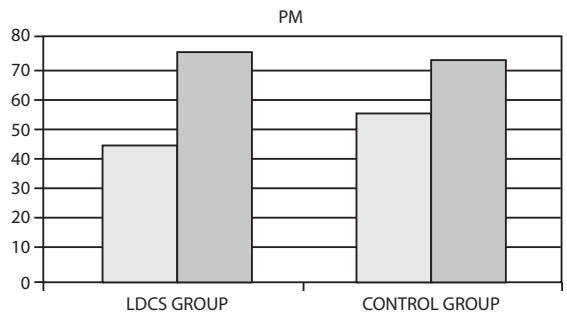

Fig. 1. *FIM scale.*

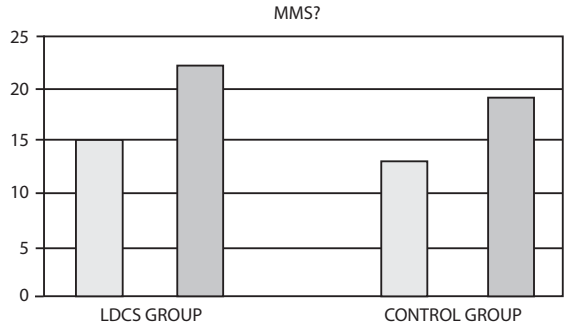

Fig. 2. *MMSE.*

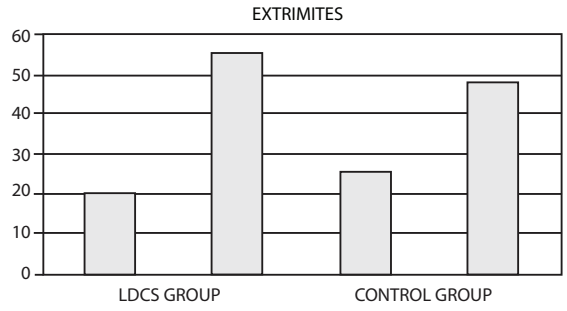

Fig. 3. *Extremities Motricity Index Scale.*

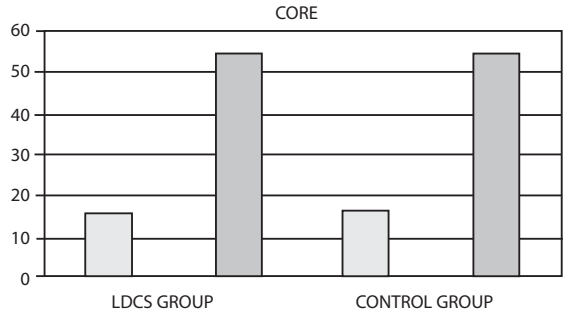

Fig. 4. *Core Motricity Index Scale.*

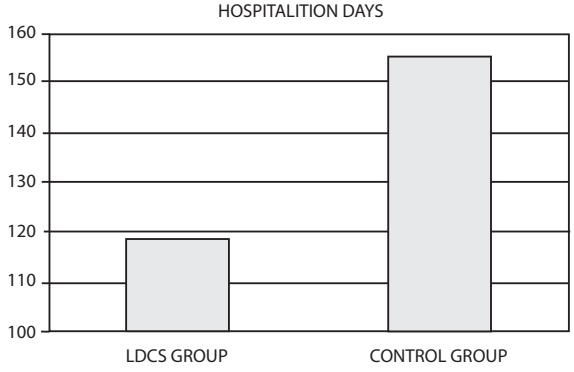

Fig. 5. *Number of Hospitalization Days.*

CONCLUSIONS: Fifteen sessions of anodal t-DCS to the ipsilesional MI appear to be safe in non-acute stroke patients. t-DCS application seems to improve the clinical outcome of the patients and reduce the days of hospitalization of post-stroke patients. The noninvasive nature of the method, the low cost of the devices, the portability and the ease of use can make it a very popular method in the neuro-rehabilitation clinics.

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9

COMPUTATIONAL INVESTIGATION OF THE INTERACTIONS IN HUMAN SERUM ALBUMIN COMPLEXES WITH FULLERENES

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Human serum albumin (HSA) is an abundant protein in blood plasma[1] and an important target in the field of pharmacokinetic and targeted drug delivery research,[2-3] owing to its integral role in ligand transport and distribution.[4] This includes fatty acids, amino acids, hormones, drugs, as well as nanoparticles (NPs).[5] Extensive experimental research has been conducted on the interactions between HSA and small organic molecules concluding that drug binding to the protein may be regulated to alter pharmacokinetics and pharmacodynamics. We expanded this knowledge to include nanoparticle–HSA interactions by investigating the binding properties of HSA complexes with fullerene NP analogs. Fullerenes display a wide variety of shapes and sizes, exhibiting great potential in numerous biological and medicinal applications,[6-8] as antibacterial, antiviral, and neuroprotective agents.[9] By means of computer simulation methods, we have elucidated the binding mechanism in fullerene–HSA complexes.[10] Our results show that fullerene-bound forms of HSA are more compact and stable compared to the apo protein. Also, binding to IIA site results in allosteric modulation of the IIIA and heme binding sites, with an increase in α-helical structure of IIIA. Fullerenes displayed high binding affinities for HSA, with values ranging from –10 to –70 kcal/mol (binding in IIA is stronger than in IIIA); therefore, HSA may be used as an effective fullerene carrier, and toxicity effects may be observed at the site of fullerene release. We have also found that fullerene derivatives with long and negatively charged groups are necessary to maximize interactions with HSA that lead to enhanced binding, therefore nanoparticle design for biological applications should consider these features.

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10

EVALUATION AND MANAGEMENT OF SYNCOPE IN THE EMERGENCY DEPARTMENT

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INTRODUCTION: Syncope is a sudden, temporary and brief loss of consciousness. Presyncope is defined as weakness, cold sweat, blurred vision and difficulty in maintaining at upright posture, without being always associated with loss of consciousness. Fainting appears with nausea, cold sweating and unspecific symptoms. The syncope is caused by transient decrease of the brain's perfusion that spontaneously and completely gets resolved requiring no resuscitation. The aim of the study is to address the prompt management of a syncopal event in the emergency room (ER).

MATERIALS - METHOD: A retrospective study analyzed the ER files during a six months period (July-December 2015) and 13 patients were found who presented with syncopal episodes. Out of 13 patients, 8 were men with a mean age of 64 years and 5 were women with a mean age of 72 years.

Triage's stratified risk method performed among the patients with syncopal incident, including medical history, physical examination, ECG (long QT), blood pressure, blood tests (+ Mg, Ca, TnI and pregnancy test). The patients were stratified as: (i) Low risk (first episode, age <40, non pathological ECG, negative history for heart disease, no trauma), (ii) Medium risk [Not first episode, age> 40, abnormal or questionable ECG, trauma, orthostatic hypotension without hypovolemia, pacemaker (even without malfunction indications) carotid hypersensitivity], (iii) High risk [medical history or indication of myocardial infarction/heart disease, arrhythmia (especially ventricular tachycardia, pauses > 3 sec), branch block, severe trauma, orthostatic hypotension with hypovolemia (hemorrhage)]. The management of the incidents in the ER is based on the ISO 2008 standards.

RESULTS: All patients were considered as high risk and an integrated clinical evaluation of an ER specialist took place, which included detailed description of the event from patient and attendants, medical history, medication, blood pressure on both upper limbs (bedridden and upright), auscultation and palpation of peripheral pulses including carotids. Furthermore, a cardiologist's, a neurologist's and a psychiatrist's assessment were performed to diagnose or exclude psychogenic syncope, epilepsy, transient cerebral ischemic attack (vertebrobasilar), or other neurological disorders, such as Parkinson's disease, respectively.

CONCLUSIONS: The hospitalization criteria for a syncopal patient include the correct diagnosis (heart disease, ECG, fatigue, trauma, family history of sudden death, tachycardia in bedridden position) and the need for specific management (set by arrhythmia, cardiac ischemia, ischemic necrosis, pacemaker, cardiopulmonary and neurological pathologies). The medication depends on the syncope's characteristics. A low risk, non-recurrent syncope does not require treatment unless the patient is considered to be at clinical risk or his profession exposes him to certain risk factors.

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I1

GLYCATED HEMOGLOBIN IS MORE IMPORTANT IN PREDICTING BONE MINERAL DENSITY THAN BONE RELATED PARAMETERS IN HEALTHY PREMENOPAUSAL WOMEN

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INTRODUCTION: Premenopausal Bone Mineral Density (BMD) is determined by genetic and other hormonal or skeletal factors related to bone turnover. The aim of this study was to investigate the effect of integrated glycemia as determined by glycated heamoglobin (HbAIc) on BMD and combine this effect with established skeletal determinants in a multiple regression model aiming to predict BMD in healthy premenopausal women.

PATIENTS AND METHODS: Forty-eight healthy premenopausal women (age 4I +/- 7 years) (BMI 24 +/- 4 kg/m2) were included in the study. Women with a family history of osteoporosis, menstrual disorders, diabetes or metabolic syndrome and glucocorticoid treatment for >I month in the past were excluded from the study. Anthropometric measurements, diet and exercise questionnaires and plasma/serum measurements for glucose, insulin, HbAIc, parathyroid hormone (PTH), vitamin D (25(OH)D), Calcium and osteocalcin were performed. The BMD of the lumbar spine and femoral neck was measured by dual energy X-ray absorptiometry. Multiple linear regression was used to assess best determinants of BMD.

RESULTS: There was a statistically significant positive correlation of HbAIc with femoral neck BMD (r=0,343, p<0,05) while no correlation was found for 25(OH)D (r=-0,0I6, p=0,9I5), PTH (r=-0,057, p=0,708) and osteocalcin (r=-0,I08, p=0,506). When lumbar spine BMD was examined no correlation was found for HbAIc, 25(OH)D, PTH or osteocalcin. Moreover no correlation was found with blood lipid parameters or uric acid for either site of DEXA measurement.

CONCLUSIONS: In a multiple regression model the use of 4 independent variables (HbAIc, PTH, 25(OH)D and osteocalcin) cannot predict the variability in femoral neck BMD of healthy premenopausal women. The only statistically significant correlation is with HbAIc and increasing HbAIc by I% predicts an increase in femoral neck BMD by 0,I85 g/cm^2.

I2

EVALUATION OF RENAL LONG AXIS ANGLE ON ^{99m}TC-DMSA SCINTIGRAPHY IN CHILDREN WITH URINARY TRACT PATHOLOGIES

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PURPOSE: There are limited published data concerning the renal long axis angle measurement in association

with renal pathologies. The aim of our study was to investigate whether the renal long axis angle is associated with urinary tract infection (UTI) and vesicoureteral reflux (VUR) with the use of Tc-99m dimercaptosuccinic acid (^{99m}Tc-DMSA) scintigraphy.

MATERIAL AND METHOD: In a 2-year-period 265 children (139 males, 126 females, mean and median age 6.2 and 4.5 years respectively) were referred to our Nuclear Medicine Department for ^{99m}Tc DMSA scan. All patients were divided in nine groups (UTI without VUR, UTI with VUR, UTI with or without VUR, VUR without UTI and VUR with or without UTI, UTI with cortical lesions, UTI without cortical lesions, VUR with cortical lesions, VUR without cortical lesions). Renal angle was determined as the angle between the longitudinal body axis of the patient and the renal long axis and was manually drawn and measured by two nuclear medicine physicians. When renal long axis could not be determined with accuracy, scans were excluded from analyses. In total 318 kidney units were included. Normality of the measured angles was assessed with Kolmogorov-Smirnov test. The agreement of the measured renal angles between the two observers was estimated with calculation of the intraclass correlation coefficient. Further analysis was performed with one and two-way analysis of variance implementing a Bonferroni correction, with the measured angles as the quantitative variables and lateralization of the measured angle (left vs right), presence or non-presence of cortical lesions, affliction on non-affliction of the kidney and disease (UTI or VUR) as factors; post-hoc power analysis was also done.

RESULTS: The measured angles were normally distributed and the intraclass correlation coefficient between the two observers was excellent at 0.90. The right renal angle was higher in affected and non-affected kidneys alike, regardless of disease (UTI or reflux; mean right: 15.2° vs left: 13.1° in unaffected and mean right: 16.7 vs left: 14.1 in affected ones; $p<0.001$ and $p=0.045$, respectively). Further analysis done separately for right and left angles showed that the higher measured angles were in the right kidneys in subjects with cortical lesions ($F: 6.98$, $p=0.008$, power=0.99 with $\alpha=0.05$). More in detail the mean±SD left measured angles with cortical lesions were 14.1°±6.3° and without cortical lesions 12.9°±4.6°, whereas the right-sided ones were 16.4°±4.5° with cortical lesions and 14.9°±3.9° without cortical lesions, respectively.

CONCLUSION: Renal angle may give useful information for the presence of renal pathologies and this work is congruent with earlier published reports, with the advantage of quantifying the renal angles separately for the right and left kidney. Further studies with large series would be needed to evaluate the application of renal long axis angle for the assessment of urinary tract system abnormalities.

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13

EVALUATION OF THE FLUCTUATION OF SERUM TSH LEVELS USING IMMUNORADIOMETRIC ASSAY IRMA IN THE FOLLOW UP OF PATIENTS WITH THYROID CANCER AFTER INTRAVENOUS ADMINISTRATION OF RECOMBINANT TSH

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INTRODUCTION: Thyroid cancer is the most common cancer of the endocrine glands and constitutes 1-

2% of all neoplasms. Usually treated with total thyroidectomy followed by diagnostic monitoring with whole body scanning. Whole body scanning requires elevated levels of TSH. Until today, in order patients to undergo radioiodine whole body scanning they were obligated to abandon their replacement therapy with T4 for a month as a result they suffered from edema, headache and other symptoms of hypothyroidism. Administration of Recombinant TSH (Thyrogen) is a method to avoid these symptoms and the suffering they cause. Aim of the present study is to evaluate the fluctuation of the levels of thyroid stimulating hormone (TSH) in the serum of patients with thyroid cancer and total thyroidectomy undergoing whole body scanning with Iodine $^{-131}$ after intravenous Recombinant TSH.

PATIENTS AND METHODS: We studied 36 patients with thyroid cancer, 26 women and 10 men average age 49 years (39 ± 8 years). Patients were monitored in the University Surgery Clinic of the University Hospital of Evros. All of them had undergone total thyroidectomy and histological confirmation of cancer. In all patient's blood samples were taken before, the first and the second day after the administration of Recombinant TSH for the evaluation of serum TSH. The TSH levels were measured by immunoradioassay (IRMA) method with I^{125} TSH kits Diasorin at in- vitro laboratory of Nuclear Medicine Dept. University Hospital of Evros, Democritus University of Thrace. The third day a radioiodine whole body scanning with tomographic SPECT γ-camera was performed. Statistical analysis was performed by the x^2- test (student test) and statistical significance was considered to be for $p < 0.005$.

RESULTS: 19 patients had metastasis in various sites. From them, patients with multiply metastasis had very high fluctuation of TSH levels in comparison with the patients with fewer metastasis (1^{st} day mean 65±14 ng/ml 2^{nd} day mean 145±28 ng/ml) ($p < 0.005$). Patients with fewer metastasis (1-2) had not very high fluctuation of TSH levels (1^{st} day mean 35±8 ng/ml 2^{nd} day mean 65±17 ng/ml) ($p < 0.005$). The rest 17 patients with no metastasis had lower fluctuation of TSH levels (1^{st} day mean 27±6 ng/ml 2^{nd} day mean 39±19 ng/ml) ($p < 0.005$).

CONCLUSIONS: Patients with metastases have higher TSH levels in the second and in the third day compared to the TSH levels of patients without metastases. Patients with multiply metastasis had very high fluctuation of TSH levels in comparison with the patients with fewer metastasis. Use of Recombinant TSH is useful because patients are not obligated to abandon their replacement therapy with T4 for a month so they avoid the painful symptoms of hypothyroidism.

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FOOD ALLERGY TESTING IN INFANTS AND CHILDREN BY DETECTION OF SERUM ALLERGENS USING RAST TEST

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INTRODUCTION: Food allergy is defined as an abnormal immune response to food. It is a complex situation affected by many different factors. A wide variety of food can cause allergy. The organism reactions to various food allergens are also diverse: respiratory, dermatological and gastrointestinal. Aim of this study is to evaluate the rate of food allergens factors in infants and children, so as, according to the results of the nutritional factor, to change and facilitate monitoring person by medical specialists.

PATIENTS AND METHODS: 143 infants and children (61 boys and 82 girls) was studied aged between 3 months and 13 years old. The most of them (112) were patients of the University Pediatrics Clinic of the University Hospital of Evros and the rest were patients of other pediatricians. All of the children had food allergy because of different reasoning. Special group were the infants (71), who had allergy to milk. In all children blood samples

were taken and after centrifugation the serum was collected and kept refrigerated at -70°C until the measurment. The F group (food group) from the list of allergens were tested by Radioallergosorbent test (RAST test) and concerns the quantification of the IgE antibodies to the specific allergen, with I^{125} allergen kits Bio-Line at in- vitro laboratory of Nuclear Medicine Dept. University Hospital of Evros, Democritus University of Thrace. Statistical analysis was performed by the x^2- test (student test) and statistical significance was considered for $p < 0.005$.

RESULTS: 79 % of the infants had milk allergy especial to the factors F76 (Alpha lactalbumin), F78 (Casein) and F79 (Gluten). 80% of the children had allergy especial to the factors F2 (Cow milk), F74 (Egg whole) or Fl (Egg white). l0% of the children were negative.

CONCLUSIONS: The identification of various types of allergens by RAST method is an accurate and sensitive test that helps in the diagnosis and proper treatment.

I5

SERUM 25 HYDROXY-VITAMIN- D LEVELS OF PEDIATRIC PATIENTS WITH BRONCHIAL ASTHMA USING THE RADIOIMMUNOASSAY METHOD (RIA)'

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INTRODUCTION: Bronchial asthma is a serious childhood disease that can cause discomfort in young patients and may have severe effects in their later life. The control of the aggravating factors of bronchial asthma may lead to the discovery of better treatments that will relief the young patients. Aim of this study is to evaluate the serum levels of 25 hydroxy- vitamin D [25(OH)D] of children patients and to correlate them with the severity of the disease's symptoms, in order to modify the pharmaceutical treatment which will improve the patient's condition.

PATIENTS AND METHODS: 85 pediatric patients (44 boys and 4l girls) was studied aged between 3 and l3 years old (median age of 8±3 years old). The most of them (62) were patients of the University Pediatrics Clinic of the University Hospital of Evros and the rest were patients of other pediatricians. All of the children had bronchial asthma because of different reasoning (mostly due to allergic reasoning and other lung diseases). In all children blood samples were taken and after centrifugation the serum was collected and kept refrigerated at -70°C until the measurment. The vitamin D status was measured by radioimmunoassay (RIA) method with I^{125}[25(OH)D] kits Diasorin at in- vitro laboratory of Nuclear Medicine Dept. University Hospital of Evros, Democritus University of Thrace. Statistical analysis was performed by the x^2- test (student test) and statistical significance was considered for $p < 0.005$.

RESULTS: In 52 patients with severe symptoms of the disease, the levels of [25(OH)D] were significantly low 0-20 ng/mL (0-50 nmol/L), in 2l patients with mild symptoms of the disease the levels were 20-40 ng/mL (50-l00 nmol/L) (hypovitaminosis) and the rest with no symptoms, had levels of [25(OH)D] > 40 ng/mL (>l00 nmol/L).

CONCLUSIONS: According to our results it is concluded that a statistically significant number ($p < 0.005$) of children who have vitamin D deficiency show severe symptoms of asthma. Pediatric patients with mild asthma have hypovitaminosis ($p < 0.005$). While pediatric patients with adequate vitamin D levels had no symptoms.

The levels of serum vitamin D are statistically significantly associated with the severity of the symptoms of asthma. It is possible to administer vitamin D supplements in pediatric patients with bronchial asthma in order to cause a reduction in the severity of disease symptoms. This requires further research.

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STUDY OF 25 HYDROXY-VITAMIN- D LEVELS IN THE SERUM OF PATIENTS WITH DIABETES MELLITUS

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INTRODUCTION: Vitamin D de ciency is a condition of increasing prevalence worldwide. Diabetes mellitus (DM) is related to vitamin D levels. In recent studies there is association with vitamin D de ciency and the risk of developing diabetes and diabetes complications. Aim of this study is to evaluate the serum levels of 25 hydroxy- vitamin D [25(OH) D] in patients with type 2 diabetes mellitus.

PATIENTS AND METHODS: We study 108 patients (66 male and 42 female) aged between 43 and 70 years old (median age of 58±12 years) with type 2 diabetes mellitus with or without diabetes complications. All were in follow up at the University Hospital of Evros. In all patient's blood samples were taken for (25-OH-D) determination. After centrifugation the serum was collected and kept refrigerated at -70 ° C until the measurement. The vitamin D status was measured by radioimmunoassay (RIA) method with I^{125}[25(OH)D] kits Diasorin at in- vitro laboratory of Nuclear Medicine Dept. University Hospital of Evros, Democritus University of Thrace. Also we studied 40 healthy individuals (blood donors) as control group. Statistical analysis was performed by the x^2- test (student test) and statistical significance was considered for $p < 0.005$.

RESULTS: Diabetes mellitus patients had lower levels of 25(OH)D than controls ($p < 0.005$). In 62 patients with severe complications of the disease, the levels of [25(OH)D] were significantly low 0-20 ng/mL ($p < 0.005$), in 28 patients with mild complications of the disease the levels were 20-40 ng/mL (hypovitaminosis) and the rest 18 with no complications, had levels of [25(OH)D] > 40 ng/mL($p < 0.005$).

CONCLUSIONS: Diabetes mellitus patients had lower levels of 25(OH)D than controls. Patients with severe complications of the disease had significantly low levels than the others. Vitamin D deficiency may be a risk factor for DM. Clinical trials with vitamin D supplementation are needed.

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SERUM 25 HYDROXY-VITAMIN- D LEVELS IN PATIENTS WITH MYOCARDIUM ISCHEMIA. CORRELATION WITH SPECT MYOCARDIAL SCINTIGRAPHY

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INTRODUCTION: The presence of hypovitamin D increases the risk of fractures, low vitamin D levels are also associated with hypertension, cancer, and cardiovascular disease. Aim of this study is to evaluate the serum levels of 25 hydroxy- vitamin D [25(OH) D] in patients with ischemic heart disease (IHD), as a prognostic factor of the severity of the disease, in correlation with SPECT myocardial scintigraphy.

PATIENTS AND METHODS: We study 36 patients (22 male and 14 female) aged between 39 and 65 years old (median age of 53±9 years) who suffer from ischemic heart disease (IHD). All the patients were from the

University Cardiology Clinic of the University Hospital of Evros. In all patient's blood samples were taken for (25-OH-D) determination and after this in everyone SPECT myocardial scintigraphy with ^{99m}Tc-MIBI and tomographic γ-camera was performed. After centrifugation the serum was collected and kept refrigerated at -70°C until the measurment. The vitamin D status was measured by radioimmunoassay (RIA) method with I^{125}[25(OH)D] kits Diasorin at in- vitro laboratory of Nuclear Medicine Dept. University Hospital of Evros, Democritus University of Thrace. Statistical analysis was performed by the Pearson correlation test and statistical significance was considered for $p < 0.005$.

RESULTS: 31 patients with reversible myocardial ischemia had low values of vitamin D 20-40 ng/mL (50-100 nmol/L). ($p < 0.005$). Therefore the very low prices associated with the progression of the disease. 5 patients who had normal myocardial scintigraphy (patients without coronary disease) had values of vitamin D to normal levels > 40 ng/mL.

CONCLUSIONS: In conclusion low vitamin (25-OH-D) levels may underlie established cardiovascular risk factors. The very low levels associated with the severity of ischemic heart disease. The determination of vitamin D levels in patients with (IHD), is essential to monitor patients in the treatment and outcome of disease.

I8

THE ROLE OF SERUM 25 HYDROXY-VITAMIN- D LEVELS IN PATIENTS WITH CORONARY ARTERY DISEASE. CORRELATION WITH SPECT MYOCARDIAL SCINTIGRAPHY

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INTRODUCTION: Recent studies have reported that low serum vitamin D levels are associated with a variety of diseases, including cardiovascular disease and in particular ischemic heart disease (IHD). Possible mechanisms underlying this association include increased inflammation, renin-angiotensin system upregulation, insulin resistance, altered lipid metabolism, and altered vascular smooth muscle growth and function that lead to hypertension, diabetes, dyslipidemia and atherosclerosis. Aim of this study is to evaluate the serum levels of 25 hydroxy- vitamin D [25(OH) D] in patients with Coronary Artery Disease (CAD),as a prognostic factor of the severity of the disease, in correlation with SPECT myocardial scintigraphy.

PATIENTS AND METHODS: We study 58 patients (36 male and 22 female) aged between 37 and 73 years old (median age of 58±9 years) who suffer from Coronary Artery Disease (CAD). The most of them (41) were patients of the University Cardiology Clinic of the University Hospital of Evros and the rest were patients of other cardiologists. In all patient's blood samples were taken for (25-OH-D) determination and after this in everyone SPECT myocardial scintigraphy with ^{99m}Tc-MIBI and tomographic γ-camera was performed. After centrifugation the serum was collected and kept refrigerated at -70°C until the measurment. The vitamin D status was measured by radioimmunoassay (RIA) method with I^{125}[25(OH)D] kits Diasorin at in- vitro laboratory of Nuclear Medicine Dept. University Hospital of Evros, Democritus University of Thrace. Statistical analysis was performed by the Pearson correlation test and statistical significance was considered for $p<0.005$.

RESULTS: 27 patients with myocardial infarction had low values of vitamin D,[(≤ 0-20 ng/mL (0-50 nmol/L)], ($p < 0.005$). In this group there is statistical significance in the relationship between very low values of vitamin D and patients with extensive myocardial infarction. ($p < 0.005$). Therefore the very low prices associated with the severity of disease and the impending death of patients. These patients might need more intensive monitoring.22 patients with reversible myocardial ischemia had low values of vitamin D 20-40 ng/mL (50-100 nmol/L). ($p < 0.005$). Therefore the very low prices associated with the progression of the disease.9 patients

who had normal myocardial scintigraphy (patients without coronary disease) had values of vitamin D to normal levels > 40 ng/mL (>100 nmol/L). (p<0.005).

CONCLUSIONS: In conclusion low vitamin (25-OH-D) levels may underlie established cardiovascular risk factors. The very low levels associated with the severity of (CAD) disease and the impending death of patients. The determination of vitamin D levels in patients with coronary artery disease is essential to monitor patients in the treatment and outcome of disease.

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OSTEOPROTEGERIN/RANKL RATIO SUFFICIENTLY REFLECTS BONE TURNOVER AND CORRELATES SIGNIFICANTLY WITH ANTIBODIES AGAINST TSH RECEPTORS IN GRAVES' DISEASE

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AIM: To estimate how sufficiently the osteoclastogenesis marker OPG/RANKL ratio [OsteoProteGerin / Receptor Activator of Nuclear factor KappaB Ligand] reflects the rate of bone turnover in patients with Graves' disease (GD) and to assess its correlation with the serum levels of TSHR antibodies [against TSH receptors], which represent a reliable indicator of GD activity.

METHODS: A total of 122 of GD patients participated in the study: 34 hyperthyroid at initial diagnosis (Group A), 42 with subclinical hyperthyroidism after 6-12 months of treatment (Group B) and 46 euthyroid after 6-12 months of treatment (Group C). Another 77 matched healthy controls were examined. Levels of OPG and RANKL were determined by a sandwich enzyme-linked immunosorbent assay (ELISA). TSH, fT3, fT4, antibodies against thyroid peroxidase (anti-TPO) and TSHR, ICTP, PICP, and osteocalcin (OC) were assayed with radiometric (RIA, IRMA, RRA) methods.

RESULTS: The serum levels of the studied bone metabolism markers in GD patients and normal controls are shown in the following table:

	Group A	Group B	Group C	Controls
ICTP (ng/ml)	17.78±5.04	10.72±2.93	7.62±2.94	6.58±3.37
PICP (ng/ml)	203.46±39.93	197.91±39.35	147.22±25.84	130.20±24.81
OC (pg/ml)	14.81±3.67	12.03±3.51	5.97±2.05	5.15±2.02
OPG (ng/ml)	177.10±32.90	138.65±18.66	110.17±15.14	81.56±12.75
RANKL (ng/ml)	94.44±31.19	73.27±26.26	18.57±4.29	15.35±5.32
OPG/RANKL	2.15±1.00	2.23±1.10	6.26±1.75	6.04±2.41

In newly presented GD patients, markers of bone turnover were significantly higher compared with normal controls (p<0.0001). PICP and OPG/RANKL did not differ significantly in Group A compared to Group B (p=0.319 and p=0.580 respectively), while the other markers did (p<0.0001). Pretreatment fT3 and fT4 levels correlated significantly with those of OPG (r=0.39, p<0.02), although not with any other marker of bone metabolism. Levels of bone turnover markers in Group B remained significantly higher than in euthyroid GD patients or controls (p<0.0001). Euthyroid GD patients under long term treatment (>6 months) tended to have lower (but not always normal) levels of bone turnover markers, suggesting on-going bone remodeling after the euthyroid state is attained. Levels of OPG were significantly correlated with TSHR antibodies (r=0.69,

p<0.005) and there was also a weaker positive correlation with fT4, fT3 and ICTP (r 0.36, 0.32 and 0.27 respectively, p<0.05). In all subgroups, bone metabolism markers exhibited a stronger significant (positive) correlation with TSHR antibodies and a weaker negative correlation with TSH, while they did not correlate with thyroid hormone status.

CONCLUSIONS:

I. Hyperthyroidism due to GD is associated with an increase of bone turnover (in favor of bone resorption as shown by the decreased OPG/RANKL ratio). Lack of correlation between markers of bone turnover and initial fT3 and fT4 levels, suggests that after a certain degree of stimulation by thyroid hormones, markers of bone metabolism are no further affected by them.

2. Subclinical hyperthyroidism after 6 months of treatment is associated with a persistent increase of bone turnover markers and efforts should be made to reduce the risk of bone mass loss.

3. Attainment of euthyroidism is accompanied with amelioration/normalization of bone turnover parameters (OPG sustaining a longer increase, seemingly to counterbalance the effects of the activated bone resorption preceded).

4. TSHR antibodies serum levels, while not correlating with thyroid hormone status, they quite reliably reflect bone remodelling, suggesting a direct, rather independent action of TSHR signalling on bone metabolism, especially in hyperthyroidism (the presence of TSHRs on both osteoblasts and osteoclasts may be involved in the negative regulation of osteoclastogenesis). Thus, TSHR antibodies might be used not only in predicting the clinical outcomes of GD patients but also in monitoring their bone metabolism.

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ASSESSMENT OF rCBF USING ^{99m}TC-HMPAO SPECT BRAIN SCAN IN PATIENTS WITH PARKINSON'S DISEASE

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INTRODUCTION: Parkinson's disease (PD) is a progressive degenerative disorder of the central nervous system that affects about one percent of the population over 60 years old. PD is generally featured by loss of dopaminergic fibers in brain's basal ganglia. ^{99m}Tc-hexamethylpropylene-amine-oxime (HMPAO) is a lipophilic agent, which has been used to determine the regional cerebral blood flow (rCBF), when functional brain imaging with single photon emission computed tomography (SPECT) is performed. The aim of this study is to investigate the potential presence of rCBF alterations in PD patients that might be used for clinical prognostic value purposes.

METHODS: In a 3-year-period, 46 patients were referred to our department for functional brain imaging

with ^{99m}Tc-HMPAO. Fourteen patients, nine men and five women with established diagnosis of PD were included. Mean age was 68.1 (±8.3) years, while the mean administered dose was 500-900 MBq (18.9±3.8 mCi/per patient). Eleven out of fourteen patients had a history of organic psychosyndrome. All patients after lying in a comfortable supine position, with their eyes open for almost half an hour in a quiet, dimly-lit room, were intravenously injected. Tomographic imaging started fifteen minutes after injection. Using the standardized methods of processing and filtering, regional CBF images were obtained. Twenty regions of interest (ROIs) were drawn in three projections (longitudinal, sagittal and coronal) comprising three different axis levels (whole cerebellum, cortical/subcortical regions, supraventricular level) in each of them. Since the radionuclide's deposition into the brain is proportional to the blood flow, the counts density in every ROI represents the relative rCBF, after normalization to the density of a region of reference (cerebellum). A group of fourteen historical patients (2 men and 12 women, mean age: 49.3±12.7) with normal findings was used as the control group.

RESULTS: All statistical analyses were conducted using SPSS statistics software v20. Mean rCBF values in PD patients were lower compared to controls in all regions. Significance for all statistical tests was predetermined at $p<0.05$. Shapiro-Wilk normality test revealed non-parametric distribution of rCBF values in left posterior temporal, right visual cortex and right prefrontal and central cortex areas. Besides, non-parametric distribution was observed in the relative difference (%) of rCBF values in medium frontal, prefrontal, lateral occipital, visual, parietal, prefrontal and central cortex between the two groups. Wilcoxon test for non-parametric analyses showed statistically significant difference between the mean values of rCBF in PD patients and normal subjects at the left posterior temporal ($p=0.005$), right visual ($p=0.041$) and right prefrontal and central cortex ($p=0.008$). Moreover Student's t-test showed statistically significant difference between the mean values of rCBF in PD patients and normal subjects at the right ($p=0.0002$, 95% CI 0.053 to 0.145) and the left ($p=0.06$, 95% CI 0.027 to 0.146) medium frontal cortex, left prefrontal cortex ($p=0.067$, 95% CI -0.004 to 0.107), right anterior temporal cortex ($p=0.0002$, 95% CI 0.057 to 0.164), left anterior temporal ($p=0.0008$, 95% CI, 0.054 to 0.184), right posterior temporal ($p=0.042$, 95% CI 0.002 to 0.135 left lateral occipital ($p=0.032$, 95% CI -0.008 to 0.174), left caudate cortex ($p=0.002$, 95% CI 0.042 to 0.168), left prefrontal and central cortex ($p=0.002$, 95% CI 0.032 to 0.136), left parietal ($p=0.004$, 95% CI 0.033 to 0.160).

CONCLUSIONS: Nowadays PET/CT and DaTscan are generally used for the assessment of patients with PD. However, ^{99m}Tc-HMPAO SPECT can still be a cost effective method that provides useful information about regional cerebral blood flow in patients with PD. In our study, PD patients demonstrated significant differences in rCBF in specific brain areas. Since to date rCBF changes in Parkinson's disease have not been fully demonstrated and the accuracy of PD diagnosis is rather low (65-84%), large series of patients are needed to identify which rCBF differences are correlated to clinical symptoms or might be of clinical or prognostic value and determine the specific subgroups of patients that can benefit from this modality.

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21

PULMONARY FUNCTION TEST, SLEEP DISORDER INDEXES, SIX MINUTE TEST, AND QUALITY OF LIFE QUESTIONNAIRE, IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS – WHICH IS THE BETTER CLINICAL GUIDE?

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INTRODUCTION: The frequency of sleep breath disorders in patients with Idiopathic Pulmonary Fibrosis (IPF) remains controversial, although these patients showed different level of hypoxemia during sleep. On the other side, hypoxemia is also a result of exercise in IPF patients. Our study was carried out in order to demonstrate the status of sleep breathing events and the ability of walking on six minutes test (6m-test) in newly diagnosed IPF patients, and to identify possible correlations with sleep study, 6m-test, pulmonary function testing parameters and the quality of life.

METHODS: The 16 newly diagnosed IPF patients, completed the Saint George Questionnaire (SJQ) on admission day. Then they underwent pulmonary function tests, 6m-test and an attended overnight polysomnography study. None of the included subjects was under any of the currently available IPF-treatments or nocturnal supplemental oxygen therapy.

RESULTS: Desaturation index during sleep was statistically significant correlated to total lung capacity (p=0.03, r=0.535). The arousal index was correlated to the presentation of respiratory symptoms described in SJQ (p=0.05, r=-0.497). REM AHI was statistically significant correlated to the section from SJQ; presentation of cough (p=0.02, r=-0.584). The lowest SpO2 was statistically significant correlated to the sections from SJQ; tachypnea (p=0.01, r=-0.624) breathlessness (p=0.048, r=-0.502) sensation of dyspnea (p=0.005, r=-0.662) and the probability of getting better (p=0.02, r=-0.588).

The total walking distance from 6m-test was statistically significant correlated to the sections from SJQ; tachypnea (p=0.03, r=-0.547), the sensation of luck a good day (p=0.03, r=-0.526), a better life expectation (p=0.017, r=-0.585) and the deterioration of the activity level (p=0.04, r=-0.515). There were no correlations between 6m-test and sleep parameters.

CONCLUSION: Sleep breath disorders in IPF patients influence different parameters of their quality of life in comparison to the ability of these patients on walking (6m-test). Both of the two tests were correlated only to the sensation of tachypnea of these patients. More research is needed to identify the criteria in IPF patients that influence their quality of life and the criteria for evaluation of the response to treatment strategies.

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PREDICTIVE VALUE OF ASSESSMENT OF ELECTRICAL OSCILLATIONS IN DYNAMIC DISORDERS ELECTROPHYSIOLOGY AND MYOCARDIAL PERFUSION. PROSPECTIVE STUDY - PRELIMINARY RESULTS

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INTRODUCTION: Purpose of the present study is the evaluation of a new, non-invasive method for the assessment of myocardial ischemia. The device HeartVue TM 6s analyzes small amplitude oscillations observed in the production of electrical potentials of the heart muscle, and then depending on the size of the electrical

instability estimates the possibility of ischemic heart disease or other pathological conditions involving the heart. To assess the ability of the method to reveal the likelihood of myocardial ischemia performed in our clinic a prospective study in patients undergoing percutaneous coronary angioplasty.

METHODS: A total of 47 patients who were scheduled to undergo coronary angiography were included so far in the study which is ongoing. The indication for performing coronary angiography was stable angina symptoms or positive test induced ischemia. All patients were tested with HeartVue TM 6s before starting full cardiac monitoring (echocardiography, exercise testing, coronary angiography).

An analysis of the electrical potentials and record deviations of these analyzes as provided by the system for recording and tracking of HeartVue device in tabular recording "Myocardium and Detailing Indices". The results of the device were evaluated in the light of the final diagnosis as entered by the attending physician who was not aware of the device display.

Disorders of conduction, the presence of valvular heart disease, ventricular cardiac dysfunction and coronary events might consider significant cardiac findings that required treatment by the Specialist.

RESULTS: Of the 47 patients who underwent coronary angiography, stress test, echocardiographic control and conventional ECG was necessary and performed angioplasty at 11.

The HeartVue TM 6s device in 13 (27.6%) patients gave the change indicator because of axis and rhythm disorders, and a recommendation evaluation with exercise test for angina. In 30 (63.8%) patients the indication was abnormal electrophysiological status of the patient's myocardium and establish the need of direct control with further cardiac exams. In 8 (17%) of these were an indication for emergency specialist referral - finally seven of eight (87.5%) had severe disturbance and subjected to angioplasty.

CONCLUSION: By far the data HeartVue TM seem to assessing ischemia in patients suspected with coronary artery disease. However more data need it because both the sample is small and all patients enrolled in the study were asymptomatic and were scheduled to undertake coronary angiography without suffering from acute coronary syndrome at the time of examination.

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COMPARISON BETWEEN GLOMERULAR FILTRATION RATE (GFR) ESTIMATED BY SERUM CREATININE AND CYSTATIN-C AND 51CR-EDTA GFR IN PATIENTS WITH DECOMPENSATED CIRRHOSIS

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INTRODUCTION: Accurate assessment of renal function, i.e. glomerular filtration rate (GFR), in cirrhosis has become very important. Aim of the present study, is to compare serum creatinine (sCr)- and serum cystatin-C (cysC)-based estimated GFR (eGFR) formulae with ^{51}Chromium-EDTA (^{51}Cr-EDTA) GFR ("true GFR") in patients with stable decompensated cirrhosis.

PATIENTS AND METHODS: In 129 Caucasians patients with decompensated cirrhosis we assessed sCr-based GFRs [Modification of Diet in Renal Disease (MDRD) and chronic kidney disease–epidemiology (CKD-EPI)-sCr formulae], cysC-based GFRs [Hoek, Larsson and CKD-EPI-cysC equations] and the mathematical formulae which combined both sCr and cysC [i.e. CKD-EPI-sCr-cysC and the specific for cirrhotics formula recently proposed by Mindikoglou et al (Mindi-eGFR)]. Multivariate linear regression analysis was used for GFR predictors in our cohort.

RESULTS: The correlations between ^{51}Cr-EDTA-GFR with all mathematical formulae were good (Spearman r^2 >0.68, p<0.001). MDRD and CKD-EPI-sCr had lower bias (-4.8 and 6.6, respectively), compared to the other eGFRs, while Mindi-eGFR and CKD-EPI-sCr-cysC formulae had greater precision (17.1 and 17.3, respectively), compared to the other eGFRs. CKD-EPI-sCr and Mindi-eGFR had higher accuracy (39% and 41%, respectively), compared to the other eGFRs. The factors independently associated with the ^{51}Cr-EDTA-GFR were age, cysC and sCr, and the new derived formula had lower bias (0.89) and similar precision (17.2) and accuracy (41%) with Mindi-eGFR formula.

CONCLUSION: The specific mathematical formulae derived from patients with cirrhosis seem to provide superior assessment of renal function, compared to the conventional used sCr- and cysC-based formulae.

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ΑΝΑΡΤΗΜΕΝΕΣ ΑΝΑΚΟΙΝΩΣΕΙΣ (E-POSTERS)

ΠΑΡΟΥΣΙΑΣΕΙΣ ΠΕΡΙΣΤΑΤΙΚΩΝ

24

POST-STREPTOCOCCAL UVEITIS TO A 7 YEARS OLD BOY AFTER A THERAPY FOR DENTAL ABSCESSES

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INTRODUCTION: A 7 years old boy presented with a 30-day history of blurred vision and photophobia to the left eye. Slit-lamp biomicroscopy demonstrated conjuctival circumciliary infection and mild anterior uveitis (anterior chamber activity of cells +). Posterior segment examination showed indermediate uveitis and a fibrotic/condensated lesion of vitreous attached to the posterior surface of the lens. The optic nerve and the macula were normal. The medical history revealed that for the last 6 months the boy was on a therapy for the dental abscesses he suffered from. He had been treated with a systematic antibiotic therapy not suitable for streptococcus infection and he was on a topical therapy with steroid drops for the uveitis. The blood tests revealed high levels of antistreptolysin-O titres (ASTO).

RESULTS: The patient was started a systematic therapy with the proper antibiotic and continued the topical steroids. The uveitis started to respond two months after the beginning of the therapy. At that time the visual acuity got better and the ASTO titres started to decrease.

CONCLUSION: Post-streptococcal uveitis is a very uncommon disorder especially after dental diseases. Opthalmologists must maintain a high level of suspicion especially in childhood uveitis and not forget testing for titres of ASTO when the indication exists.

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ABDUCENS NERVE PALSY CAUSED BY AN INFLAMMATORY PROCESS LOCALISED ON THE TOP OF THE PETROUS BONE

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INTRODUCTION: A 6-year-old female patient with fever of unknown origin was referred by the pediatric clinic to our clinic because of sudden onset of diplopia. Ophthalmological examination revealed right esotropia due to right abducens nerve palsy. There were no other abnormal ophthalmological findings. The patient was subjected to magnetic resonance imaging (MRI), which showed a pathological mass in the prepontine region with extension to the right cerebellopontine angle with gradual increase in size. Surgical removal of the mass was performed and open biopsy was conducted, which revealed findings compatible with chronic necrotizing granulomatous inflammation (possibly tuberculosis). Post-operatively the patient received anti-tuberculosis treatment.

RESULTS: Post-operatively recession both of the fever and the diplopia and full recovery of eye's motility.

CONCLUSION: The intracranial lesions are a common cause of abducens nerve palsy and sudden onset of diplopia. For the differential diagnosis in children it is important to have in mind the possible inflammatory nature of these lesions, which can arise from rare and "forgotten" infections.

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JUVENILE MYASTHENIA GRAVIS (JMG) WITH OCULAR INVOLVEMENT IN A 5 YEARS OLD CAUCASIAN BOY

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INTRODUCTION: A 5 years old caucasian boy came as an outpatient for consultation. He suffered from a left ptosis that appeared 2 months ago, exacerbated with strain and more prominent during the afternoon hours. Patient had good visual acuity, no pain, diplopia or head tilt and normal extraocular muscle movements. He also complained of fatigue of lower limps presenting mainly after walking. The rest of the clinical examination was normal. In the differential diagnosis we included: a) structural, b) inflammatory, c) central nervous system causes, d) sympathetic activity, e) neuromuscular, f) thyroid diseases .We proceeded with blood tests, brain MRI, chest x-ray, electrodiagnostic testing (EDT).

RESULTS: Chest x-ray and MRI were normal. Blood tests (including thyroid hormones and auto-antibodies) were normal as well. Anti-Musk and anti-AchR were found negative. Considering the fact that antibodies can be negative in 50% of the patients with JMG and based on the strong clinical presentation, JMG was set as the diagnosis and treatment started with bromide pyridostigmine. Ptosis regressed completely and patient has been stable for the last 1,5 year.

CONCLUSIONS: Although JMG is a rare condition in the Caucasian population, it must be considered as a possibility in the differential diagnosis of a paediatric case with ptosis. Prepuberty myasthenia has better prognosis than the adults MG, it appears more often as ocular or seronegative MG, it has equal ratio male : female and with the proper treatment total regression of the symptoms can be achieved although spontaneous remission is also possible.

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CONGENITAL ICHTHYOSIS. PRESENTATION OF A RARE CASE WITH OPHTHALMIC INVOLVEMENT

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INTRODUCTION: Male infant with gestational age 36 weeks was born from parents with normal family history. The clinical examination had shown armor-like cracked skin, bilateral ectropion with chemosis of the palpebral conjuctiva, hypoplastic ears, hypoplastic arms and feet with joint flexion deformity, syndactyly, hypoplastic scrotum and penis. The infant deceased 20 days later from severe infection (sepsis).

CONCLUSIONS: Congenital ichthyosis is a rare dermatological disease, with autosomal dominant (AD) inheritance. The genetic testing reveals a mutation on the ABCA12 gene which causes a deficiency to the enzyme keratinic transglutaminase. As a result there is an overproduction of keratin cells in the epidermis, loss of elasticity and an armor-like cracked skin. The survival rate of the infants is less than 10%.

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HORNER SYNDROME OCCURRENCE IN AN INFANT WITH ESOPHAGEAL ATRESIA: AN INTERESTING CASE

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INTRODUCTION: The acquired pediatric Horner syndrome is associated with interruption of the oculosympathetic pathway. Our purpose is to present an interesting acquired paediatric Horner syndrome case in an infant with congenital esophageal atresia. A male infant was diagnosed with congenital esophageal atresia of big gap without tracheoesophageal fistula during prenatal tests. At the second month of life the infant underwent stomach relocation with cervical coloboma anastomosis. Postoperatively chylothorax occurred and a bullau tube was inserted. During the following postoperative period unilateral left eyelid ptosis was observed.

RESULTS: Ophthalmological evaluation found left eyelid ptosis, miosis and enophthalmos, findings that were attributed to acquired postoperative Horner syndrome. Right pupil's reaction to light was normal, whereas left pupil's reaction to light was weak. Eterochromia iridis was not observed.

CONCLUSIONS: The current report of acquired pediatric Horner syndrome is an important and unique report correlated not only with the previous operation and the perioperative history of the patient but also with the possible mechanisms involved in its pathogenesis that affect the future prognosis.

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RETROBULBAR HEMANGIOMA OF THE ORBIT IN A NEONATE - CONFRONTATION

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INTRODUCTION: A premature neonate at the gestational age of 33 weeks and birth weight of 1420 gr, presented at the 10th day of his life severe proptosis of the left eye which was clinically attributed to retrobulbar hemangioma of the orbit. The radiological examinations (U/S, MRI) confirmed the clinical estimation. The opthalmological and fundus examination were normal in both eyes although in the left eye the proptosis was gradually increasing and the radiological examinations showed that the optic nerve had began to be suppressed.

RESULTS: The child was given propranolol as a therapy, with excellent results. The lesion and the proptosis were significantly regressed. The dose of the medicine was readjusted according to the increasing weight of the child. Four months later the proptosis can be hardly seen.

CONCLUSION: Propranolol as a therapy for the orbital hemangiomas gives us excellent results and sometimes can be salutary for the neonates' vision without significant side effects.

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RETINAL ASTROCYTIC HAMARTOMA IN A 1.5-MONTH-OLD INFANT AFFECTED BY TUBEROUS SCLEROSIS

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INTRODUCTION: A 1.5-month-old infant boy presented at the pediatric emergency department of our hospital with afebrile infantile convulsions. Clinical examination, cranial imaging with CT and MRI scans and heart ultrasonography revealed tuberous sclerosis. Eye examination, including fundoscopy was requested.

RESULTS: Fundoscopic examination of the right eye demonstrated an elevated gray-yellowish lesion close to the optic nerve head, which was consistent with the appearance of retinal astrocytic hamartoma. Ocular ultrasound B-scan showed a juxtapapillary hamartoma protruding into the vitreous. New thin-section 3D MRI of the orbit revealed a 2mm diameter lesion in the posterior pole of the right eye, corroborating with the clinical and ultrasonographic features. Left eye was normal.

CONCLUSIONS: To our knowledge, cases of retinal astrocytic hamartomas at such a young age are rarely reported. Retinal astrocytic hamartomas typically remain stable throughout life, but sometimes may also exhibit acute growth. Therefore, an early diagnosis is important in the monitoring and management of these conditions.

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POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY (PET/CT) SCAN IS A USEFUL TOOL FOR THE MANAGEMENT OF UNSPECIFIED AORTITIS

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INTRODUCTION: Large vessel Vasculitis (LVV) is a potentially life-threatening autoimmune mediated disease. According to the current classification criteria (Chapel-Hill 1992), LVV can be presented as a primary condition, or in the context of a systemic autoimmune/inflammatory disease. Pathophysiologically, infiltration of large vessel's wall with immunocompetent cells may result in aneurysm formation and fatal disruption of the vessel. Clinical suspicion, diagnosis and follow up during treatment poses a challenge to the clinician since definite diagnosis by tissue biopsy is usually unfeasible.[1]

On this context, nuclear medicine diagnostic methods assessing chronic inflammatory conditions, such as the18F-fluordeoxyglucose (18F-FDG) PET/CT scan, can be a useful tool in the diagnosis and follow up of patients with LVV.

CASE REPORT: A 56-year-old Greek female was admitted for investigation of possible LVV, after coronary bypass artery graft (CBAG) for triple vessel disease where macroscopic signs of inflammation (edema, friable tissue) of aortic root were noted by the surgeon. The patient had not other clinical or laboratory findings of LVV (normal CRP, ESR and WBC) and no predisposing factors for atheromatic disease. Since causes of secondary aortitis (rheumatoid arthritis, seronegative spondyloarthropathies, syphilis) were excluded, differential diagnosis mainly included giant cell arteritis.

A PET/CT scan (2013) confirmed isolated inflammation of the aorta (uptake of 18F-FDG by the aortic wall). The patient underwent a boost treatment with high doses of corticosteroids and azathioprine with the diagnosis of aortitis. After adequate treatment, clinical status and laboratory findings were inconclusive for disease remission. During the follow up standard of care maintenance regimen, the patient presented several episodes of stable

angina with no elevation of inflammatory indexes for another time. A new PET/CT scan was performed (2016) revealing signs of residual inflammation of aortic root.

Results were diagnostic of disease persistence and treatment was re-designed on these grounds.

DISCUSSION: Aortitis is a life threatening condition and difficult to diagnose. Protocols investigating LVV are still under evaluation. Moreover, temporal – granulomatosus LVV without clinical/laboratory/imagine and/or histopathological findings is a rare but well described manifestation. Corticosteroids and immunosuppressants are the cornerstone of treatment but indices of efficiency have not yet been established.

The immunopathology basis of the disease has been recently elucidated.[2] ThI7 cells can be suppressed, achieving clinical remission, but ThI cells can remain in latent activity resulting in continuing life threatening re-modeling of the aorta.

PET/CT can be the examination of choice in cases of vasculitic inflammation, of aortic abdominal aneurysms, vascular graft infections or chronic periaortitis. PET/CT provides a metabolic functional image of the vessel wall before structural changes can be observed by conventional imaging techniques such as MRI and CT scan.[3] PET/CT is considered to be a novel tool with high sensitivity for the diagnosis, assessment of disease burden, response to treatment and follow-up of patient with aortitis.[3,4] Until now there is no gold standard examination for the diagnosis of LVV in the absence of biopsy.

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EVALUATION OF PULMONARY EMBOLISM IN AFIBRINOGENEMIC PATIENT – CASE REPORT

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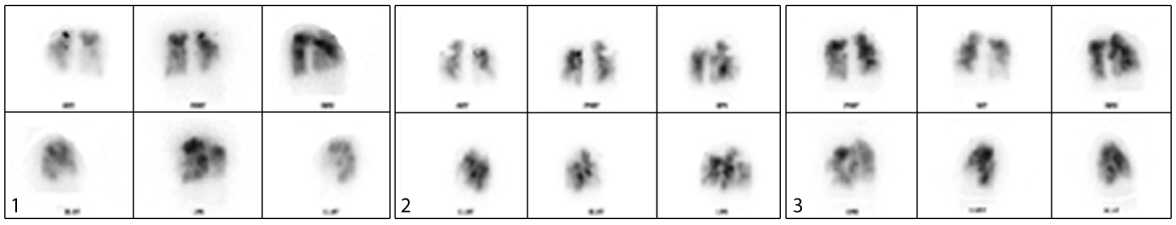
Afibrinogenemia is a very rare autosomal recessive bleeding disorder, defined either as a functional disorder of plasma fibrinogen or as complete absence of detectable fibrinogen levels in plasma. Approximately, one new case of afibrinogenemia is appearing per one million births. Afibrinogenemic patients experience bleeding tendency of varying severity from neonatal age. The first most usual hemorrhagic symptom is uncontrolled bleeding from the umbilical cord after birth. Bleeding manifestations are observed from mucosal surfaces - especially epistaxis, menorrhagia and bleeding from the oral cavity - from musculoskeletal system, gastrointestinal system and urinary tract throughout life. The original description of the disorder was given in 1920 and since then a few hundreds cases have been reported. Despite the fact that the patients with afibrinogenemia are facing the constant risk of excessive bleeding, a small but existent percentage of them may also experience thrombotic episodes. Although there is essentially total lack of plasma fibrinogen, thromboembolism can take place. The pathogenetic process of this medical paradox is not accurately known but literature's data indicate that the pathogenesis of thrombotic formation is probably multifactorial and is determined by exogenous and endogenous risk factors such as thrombophilia, infusion of fibrinogen as replacement therapy, trauma, immobilization or pregnancy. It is important to mention that thromboembolism may occur either spontaneously or in association with



Figl. *First ^{99m}Tc MAA Scan: Initial perfusion scan reveals heterogeneity of radiopharmaceutical distribution, segmental and subsegmental perfusion defects in both lungs, especially in the left lung. In addition shows hyperemic regions indicative of pulmonary redistribution bllod flow to non-occluded areas.*

Fig2. *Second ^{99m}Tc MAA Scan: Repeat perfusion scan after 2 weeks on subcutaneous LMW heparin, shows reduction in the extent of the previous defects in both lungs and improvement of the perfusion.*

Fig3. *Third ^{99m}Tc MAA Scan:Third perfusion scan after 2 months on subcutaneous LMW heparin demonstrates new subsegmental perfusion defects in both lungs.*

fibrinogen substitution therapy. Management is extremely difficult but also challenging due to the precarious balance between hemorrhage and thrombotic risk in these patients.

We report a case of a 29 years old female with afibrinogenemia treated with fibrinogen concentrates who presented with 2 episodes of pulmonary embolism (Figs I-3) during a 3 months period for which low molecular weight heparin (enoxaparin) was administered.

The patient history includes multiple incidents of knee and elbow joint hemarthrosis, intraperitoneal hemorrhage, cryoglobulinemia, vasculitis, bilateral renal artery stenosis, bowel perforation, DVT of left internal jugular and subclavian vein, HCV infection and chronic renal failure undergoing hemodialysis over one year.

The report of this case is aiming to emphasize the thrombotic complications that can occur in afibrinogenemia, to trigger discussion and draw conclusions regarding the management issues involved.

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'GLOVE' SIGN ON BONE SCAN AS A RESULT OF INTRA-ARTERIAL INJECTION IN A PATIENT WITH PROSTATE CANCER

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BACKGROUND: In some rare cases an asymmetrical uptake of the radiotracer may be found on bone scintigraphy. The "glove" sign represents the incidental intra-arterial injection of a bone-imaging radionuclide tracer into the antecubital fossa. When interpreting a bone scan, this artifact should be taken into account because it can cause confusion concerning the diagnosis.

CASE REPORT: A 57-years-old male patient was shown to have a prostate specific antigen level of 3.2 ng/mL in a routine check-up. The patient underwent prostate biopsy which revealed Gleason score 6 (3+3) adenocarcinoma. Ultrasound showed a prostate volume of 46 mL while postvoid residual urine was 17 ml. Nothing remarkable was found in patient's history. The patient was referred to our department for a bone scan with ^{99m}Tc-Methyl-diphosphonate (^{99m}Tc-MDP). After iv injection of ^{99m}Tc-MDP (740 MBq), the acquired delayed images showed diffusely increased uptake at the right forearm, especially on the radial half of the wrist, the first, second and third metacarpals and the proximal phalanges (Fig. 1). The finding could not be explained by the clinical history. Even though the findings could mistakenly lead to the diagnosis of metastases, the nuclear medicine stuff ascertained the accidental intra-arterial injection, so no confirmatory three phase bone scintigraphy was necessary.

CONCLUSION: Bone seeking agents when accidentally intra-arterially injected can result to diffusely increased uptake distal to the injection site. Thus a variety of images can be seen depending on the injected artery. Unusual images may cause confusion in diagnosis and the need to differentiate from metastasis or other skeletal pathologies can arise. Beyond and further from an adequate clinical history, nuclear medicine physicians should have in mind the possibility of an intra-arterial injection when non-expected images are presented in bone scan with ^{99m}Tc-MDP.

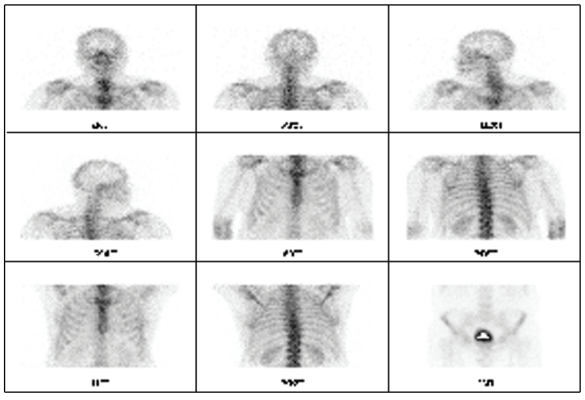

Fig 1. *Bone scan at 3h p.i. revealed diffusely increased uptake at the right forearm, especially on the radial half of the wrist, first, second and third metacarpals and the proximal phalanges.*

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ΑΝΑΡΤΗΜΕΝΕΣ ΑΝΑΚΟΙΝΩΣΕΙΣ (E-POSTERS)

ΑΝΑΣΚΟΠΙΚΕΣ ΕΡΓΑΣΙΕΣ

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RADIOPHARMACEUTICAL SELECTION FOR INFLAMMATION AND INFECTION IMAGING

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67Ga-citrate and leukocytes, labelled either with 111In-oxine or with 99mTc-HMPAO, are the most widely used radiopharmaceuticals for imaging of inflammation and infection. The selection between gallium and leukocyte imaging mainly depends on the clinical question and the reported efficiency of each agent for each indication. Generally, the use of radiolabelled leukocyte imaging is considered to be adequately sensitive and more specific than gallium imaging for most of the common indications. However, gallium imaging is still considered advantageous in certain clinical settings. In particular cases, each of these methods can be combined with other radionuclide scans such as a three-phase bone scan or a bone marrow scan to improve their accuracy.

The most common indications for inflammation and infection imaging include osteomyelitis, diabetic foot, prosthetic joint infections, inflammatory bowel disease, sarcoidosis and fever of unknown origin.

In osteomyelitis, imaging with 99mTc-HMPAO leukocytes shows higher accuracy than the combination of three-phase bone scan with gallium imaging. The accuracy of leukocyte imaging is further improved by combining it with a bone marrow scan with 99mTc-sulfur colloid. The exception is vertebral osteomyelitis, where 67Ga-citrate scintigraphy seems to be advantageous.

In prosthetic joint infections, leukocyte imaging combined with bone marrow imaging is the gold standard, as it shows higher accuracy than the combination of gallium imaging with three-phase bone scan.

In diabetic foot, imaging with 99mTc-HMPAO leukocytes is the preferred method due to higher specificity and higher resolution.

In inflammatory bowel disease assessment, 99mTc-HMPAO leukocytes have been shown advantageous due to higher resolution, provided that imaging takes place 1-2 hours after injection.

In sarcoidosis, 67Ga-citrate scintigraphy is usually preferred for diagnosis and assessment of therapeutic results.

Similarly, in fever of unknown origin, 67Ga-citrate is most widely used. There is evidence that FDG PET-CT might be more sensitive, but low specificity and high cost currently limit its use in this context.

Gallium imaging can also substitute leukocyte imaging in cases of neutropenic or immunocompromised patients, or in low-grade chronic infections, where the participation of leukocytes in the inflammation process is expected to be low. Imaging of osteomyelitis and prosthetic joint infections has also been attempted with 99mTc-radiolabelled antigranulocyte monoclonal antibodies or fragments. This technique is preferred due to easy and reliable preparation of the radiopharmaceutical.

In everyday practice, various technical matters might play a role in the selection. Therefore, a certain choice may also depend on the Nuclear Medicine Department's resources and qualification standards.

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BIOMETRIC DATA & ETHICS

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E-health era in European Union (EU) is approaching rapidly and its most innovative vision are Personal Health Systems[1]. Many scientific fields such as Information and Communications Technology (ICT), Micro-Opto-Electro-Mechanical Systems (MOEMS), Nano-Electro-Mechanical systems (NEMS), Nanorobotics and Biometrics elaborate in order to present complete solutions of ubiquitous person-centered healthcare services.

Biometrics intend on their part to provide intelligent identification, authentication and monitoring techniques using multi-sensors that will process multi-dimensional data resulting in a holistic representation of a person's physical, contextual and psychological status from a distance or on-the-move.

Modern generation biometrics[2] include face, gait, smile, voice, handwriting, signature, electroencephalogram, electrooculogram, electromyogram, dna, body odor, keystroke or mouse dynamics, online behavior recognition and more.

Biometric data are already implemented in public and private sector worldwide: medical/ social and natural science/forensic applications, e-commerce, e-banking, distant learning, ATM transactions, ticket tag systems, access control systems, governmental applications i.e. us-visit, Prüm treaty, reverse image search engines etc. Also possible is the simultaneous combination of different biometric databases (Multibiometric Databases) or linking those with other databases (Multimodal Systems) such as credit card, social security and e-health.

The main issue is whether there are laws[3] in Europe that address biometric data. Unfortunately the answer is no. EU's attitude is rather unclear. While it recognizes the need to modernize laws, it simultaneously allows the use of biometric data on our personal computers, laptops and mobiles. There is a strong concern that technology is the key driver and that the moral and legal dimension are just an afterthought. This concern grows as the public is expected to use these technologies before the laws for proper data protection and privacy have been enacted or even discussed. Moreover it's considered difficult to implement appropriate laws in already established systems.

There is a plethora of questions stated[4]. Some of these relate to the limitation of human rights and a breach in security, confidentiality and protection of biometric data. Storage, management and processing of the data and also transparent procedures are still unsolved issues. Misuse of such data, data mining and profiling for unauthorized purposes are likely to occur. Will there be a patient's right to consent, access his/her data, object or even delete his/her own data? The most common social issue is undoubtedly the fear of a non-stop controlling and monitoring regime.

Biometric data are data that identify an individual. Thus they must be considered personal data and protected as such. Furthermore in the cases that they relate to an individual's health or result from an individual's physical, biological or physiological characteristics, they must be considered as sensitive data and regulated by clear and sufficient laws.

Human rights and principles of Bioethics i.e. respect for autonomy, beneficence, nonmaleficence and justice should be respected. EU must undertake the process of implementing new and effective laws that will explicitly define biometric data and include them as sensitive where needed, thus safeguarding people's dignity in a digitized society that the Internet of Things (IoT) demands.

The word biometrics derives from the greek words "Bios" which reflects human life and "Metro" that means "to measure". Bios has a deep meaning and encompasses our existence's purpose, our ideas, values, attitudes, beliefs and experiences whether physical or emotional. It is debatable whether real Bios can be measured, but in any case Bios is a person's very own identity, character, life, the human being himself; and should only belong to that person.

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HEALTH EFFECTS OF COSMIC AND MEDICAL RADIATION

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INTRODUCTION: Most of the radiation dose we receive is from naturally occurring sources—most of this is from radon and secondly from cosmic radiation. The next largest dose is from medical radiation. On the ground, cosmic radiation makes up on average about 13% of our total exposure and medical radiation globally accounts for about 21% of our total exposure. Cosmic radiation consists of energetic charged particles, that originate from events beyond our solar system and from the sun, and varies in different parts of the world due to differences in elevation and to the effects of the earth's magnetic field. The most significant source of man-made radiation exposure to the public is from medical procedures, such as diagnostic X-rays, nuclear medicine, and radiation therapy. X-ray based methods of medical imaging include conventional X-ray, angiography, computed tomography (CT) and mammography. Molecular imaging is used in nuclear medicine and uses small amounts of radioactive markers, called radiopharmaceuticals.

PURPOSE: The purpose of our study is to inform about health effects of cosmic and medical radiation, after a comprehensive literature review.

RESULTS: The dose from cosmic radiation varies in different parts of the world due to differences in elevation and to the effects of the earth's magnetic field. The additional annual cosmic radiation dose that the world's population receives is an average of 0.4 millisieverts(mSv). These cosmic rays are too low-energy to cause any serious health effects, aside from a few genetic mutations (that can lead to cancer) in combination with other harmful factors. By far, the aircrew generally receive is 2-5 mSv annually. In addition, the relevant biological effect of medical imaging is mainly secondary to ionization. The risk of developing cancer is slightly increased after medical radiation exposure and the likelihood increasing as the dose increases. Children are at additional risk because they are inherently more radiosensitive than adults and live longer, so the effects of radiation have more time to become visible.

CONCLUSION: The human population is exposed to ionizing radiation from many sources. The cosmic radiation is generally unavoidable for the population. Further research is needed to clarify the risk of cancer in relation to cosmic radiation. The benefits of medical radiation are obvious and undeniable, but the inappropriate use can lead to unnecessary radiation doses and cause potential health hazards.

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ΕΜΒΟΛΙΑ ΣΕ ΑΝΟΣΟΚΑΤΕΣΤΑΛΜΕΝΟΥΣ ΑΣΘΕΝΕΙΣ

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ΕΙΣΑΓΩΓΗ: Το ποσοστό των ανοσοκατεσταλμένων ασθενών αντιστοιχεί στο 3.6% του γενικού πληθυσμού και παρουσιάζει αυξητική τάση τα τελευταία χρόνια λόγω του αυξημένου επιπολασμού της λοίμωξης με τον ιό

της ανθρώπινης ανοσοανεπάρκειας και της ευρείας χρήσης της ανοσοκατασταλτικής θεραπείας. Οι ανοσοκατεσταλμένοι ενήλικες ασθενείς βρίσκονται σε αυξημένο κίνδυνο εμφάνισης λοιμώξεων, που συχνά σχετίζονται με ευκαιριακά παθογόνα και έχουν αυξημένη νοσηρότητα και θνητότητα. Η εφαρμογή ενεργητικής ανοσοποίησης με εμβόλια εμφανίζει ορισμένες ιδιαιτερότητες λόγω ανεπαρκούς απάντησης του ανοσιακού συστήματος στα ανοσογόνα και αυξημένης πιθανότητας νόσησης από εμβόλια με ζώντες μικροοργανισμούς.

ΥΛΙΚΑ - ΜΕΘΟΔΟΣ: Ανατρέξαμε στη διεθνή βιβλιογραφία με σκοπό να καταγράψουμε τις ενδείξεις και τους περιορισμούς των εμβολιασμών σε ανοσοκατεσταλμένους ασθενείς. Συγκεντρώσαμε τις πιο πρόσφατες κατευθυντήριες οδηγίες σχετικά με τον εμβολιασμό ανάλογα με το βάθος της ανοσοκαταστολής και το υποκείμενο νόσημα. Ιδιαίτερη έμφαση δόθηκε σε ασθενείς με αιματολογική νόσο και σε αυτούς που βρίσκονται σε φαρμακευτική ανοσοκαταστολή.

ΑΠΟΤΕΛΕΣΜΑΤΑ: Η χορήγηση νεκρών εμβολίων θεωρείται γενικά ασφαλής, ανεξάρτητα από το επίπεδο της ανοσοκαταστολής, ωστόσο η απόκριση του ανοσιακού συστήματος είναι ελαττωμένη και πιθανόν, ανεπαρκής. Η χορήγηση εμβολίων με ζώντες εξασθενημένους μικροοργανισμούς υπόκειται σε αυστηρότερους περιορισμούς ανάλογα με τη βαρύτητα της ανοσοανεπάρκειας. Οι εμβολιασμοί πρέπει να προηγούνται τουλάχιστον για 4 εβδομάδες για τα ζώντα και 2 εβδομάδες για τα νεκρά εμβόλια, πριν την εφαρμογή προγραμματισμένης ανοσοκαταστολής, χωρίς βέβαια αυτό να καθυστερεί την έγκαιρη αντιμετώπιση του υποκείμενου νοσήματος.

ΣΥΜΠΕΡΑΣΜΑΤΑ: Η αυξημένη συχνότητα ανοσοκαταστολής στον γενικό πληθυσμό καθιστά αναγκαία την εφαρμογή στρατηγικών για την πρόληψη των λοιμώξεων και τη μείωση της νοσηρότητας σε αυτούς τους ασθενείς. Τα εμβόλια αποτελούν βασικό κομμάτι αυτής της προσπάθειας και δεν πρέπει να παραβλέπονται. Το πρόγραμμα εμβολιασμών θα πρέπει ακολουθεί τις διεθνείς συστάσεις, ώστε να σταθμιστούν οι ωφέλειες και οι κίνδυνοι των εμβολίων σε συνθήκες ανοσοκαταστολής.

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ΒΙΟΗΘΙΚΗ "ΞΕΝΑΓΗΣΗ" ΤΩΝ ΜΕΤΑΜΟΣΧΕΥΣΕΩΝ

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ΕΙΣΑΓΩΓΗ: Η συζήτηση για τις μεταμοσχεύσεις οργάνων αγγίζει πολλά από τα βαθύτερα ζητήματα της βιοηθικής. Η βιοηθική εξετάζει την ηθική διάσταση των προβλημάτων, που ανακύπτουν από την κλινική εφαρμογή των βιοϊατρικών ερευνών, συνενώνοντας τις βιολογικές επιστήμες με την ηθική και συγκεκριμένα με την συνδρομή ανθρωπιστικών επιστημών, όπως της νομικής, φιλοσοφίας, κοινωνιολογίας, θεολογίας. Οι ηθικοί και δεοντολογικοί προβληματισμοί που αναφύονται σε σχέση με τις μεταμοσχεύσεις, έχουν ως επίκεντρο το γεγονός ότι για πρώτη φορά στην ιστορία της ιατρικής επιστήμης, η ζωή ενός ανθρώπου εξαρτάται απόλυτα από το θάνατο ή την ελεύθερη βούληση άλλου για προσφορά οργάνου. Σκοπός της παρούσης εργασίας είναι να αναδείξει ότι η μεταμόσχευση δεν αποτελεί μια απλή ιατρική θεραπευτική μέθοδο, αλλά μια σύνθετη ιατρική πράξη, που ξεπερνά τα σύνορα της κλασσικής ιατρικής και εισέρχεται σε πεδία διεπιστημονικής προβληματικής.

ΥΛΙΚΟ – ΜΕΘΟΔΟΣ: Εφαρμόστηκε η ανασκόπηση της τρέχουσας ελληνικής, διεθνούς, διαδικτυακής επιστημονικής βιβλιογραφίας, κλασικών πηγών φιλοσοφίας και Πατερικών κειμένων, προκειμένου να αναδυθούν οι όποιοι βιο-ηθικοκοινωνικοί προβληματισμοί.

ΣΥΜΠΕΡΑΣΜΑΤΑ: Οι μεταμοσχεύσεις ιστών και οργάνων δεν αποτελούν ένα αμιγώς βιοϊατρικό θέμα.

Έχουν, μεταξύ των άλλων, προεκτάσεις πνευματικής φύσεως· και αυτό γιατί οι μεταμοσχεύσεις αναφέρονται στο μυστήριο της ζωής και του θανάτου και εγγίζουν το ιερό της ψυχοσωματικής συμφυΐας του ανθρώπου. Βασίζονται στη δυνατότητα καλλιέργειας σχέσεων αγάπης, συναλληλίας και αμοιβαίου ενδιαφέροντος των ανθρώπων.

Μόνον έτσι βρίσκονται τα μοσχεύματα. Όλα αυτά αφορούν άμεσα την Εκκλησία. Εξάλλου οι μεταμοσχεύσεις θα ζήσουν, μόνον όταν μάθουμε να δίνουμε· σίγουρα θα πεθάνουν, όταν θέλουμε να παίρνουμε. «Μακάριόν εστί μάλλον διδόναι ή λαμβάνειν».

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Η ΔΙΑΧΕΙΡΙΣΗ ΤΟΥ ΔΕΥΤΕΡΟΥ ΣΗΜΑΤΟΣ ΤΗΣ ΑΝΟΣΙΑΚΗΣ ΑΠΟΚΡΙΣΗΣ ΣΤΗ ΘΕΡΑΠΕΙΑ ΤΗΣ ΡΕΥΜΑΤΟΕΙΔΟΥΣ ΑΡΘΡΙΤΙΔΑΣ (ΡΑ)

Τρύφωνος Α, Χρηστίδης Π, Μπούρα Π.

Ιατρική Σχολή Αριστοτελείου Πανεπιστημίου Θεσσαλονίκης

Κεντρικό ρόλο στην διαιώνιση της φλεγμονώδους διαδικασίας που εξελίσσεται στο μικροπεριβάλλον του αρθρικού υμένα στην Ρευματοειδή Αρθρίτιδα (ΡΑ) κατέχει η ενεργοποίηση του βοηθητικού Τ-λεμφοκύτταρου ($CD4^+$Th). Για την ενεργοποίηση και τον κλωνικό πολλαπλασιασμό του $CD4^+$Th απαραίτητο είναι πέρα από το πρωτογενές σήμα (MCH/Ag – TCR) και η επαγωγή του δεύτερου σήματος. Η καλύτερα μελετημένη οδός δευτερογενούς μηνύματος στην συνομιλία ΑΠΚ – Τ λεμφοκυττάρου αφορά τη σύνδεση του μορίου CD28 από πλευράς του $CD4^+$Th με το αντίστοιχο μόριο CD80/86 από πλευράς του αντιγονοπαρουσιαστικού κυττάρου (ΑΠΚ), που οδηγεί σε ενεργοποίηση της Τ- διαμεσολαβούμενης ανοσιακής απόκρισης. Αντίθετα, η σύνδεση του μορίου CTLA-4 του $CD4^+$Th με το μόριο CD80/86 του ΑΠΚ οδηγεί το $CD4^+$Th σε ανέργεια (αναπαντητικότητα).

Θεραπευτικές προσεγγίσεις που στοχεύουν στην επίτευξη ανέργειας μέσω της χορήγησης βιολογικών παραγόντων, έχουν ως δραστικό στοιχείο του μορίου τους, τμήμα του υποδοχέα CTLA-4. Κύριος εκπρόσωπος της παραπάνω θεραπευτικής προσέγγισης είναι η ανασυνδυασμένη πρωτεΐνη αμπατασέπτη (Abatacept - CTLA-4Ig). Στο μόριο αυτό συνδυάζονται το εξωκυττάριο τμήμα του υποδοχέα CTLA-4 και το σταθερό τμήμα (Fc) της ανθρώπινης ανοσοσφαιρίνης IgG. Η αμπατασέπτη αναστέλλει την παραγωγή προφλεγμονώδων κυτταροκινών (IL-1, IL-6, TNFa) και παρεμποδίζει την ενεργοποίηση των $CD4^+$Th λεμφοκυττάρων. Συγκριτικά με τις υπόλοιπες βιολογικές θεραπείες πλεονεκτεί ως προς την αναστολή της φλεγμονώδους διαδικασίας με περισσότερο στοχευμένο μηχανισμό.

Σε κλινικό επίπεδο έχει καταδειχθεί ότι η αποτελεσματικότητα του μορίου CTLA-4Ig είναι ισοδύναμη με αυτή των αντι-TNF παραγόντων και δύναται να χρησιμοποιηθεί σε ασθενείς που οι συνοσηρότητές τους απαγορεύουν τη χρήση των αντι-TNF παραγόντων. Γι'αυτό το λόγο άλλωστε, συστήνεται σε ασθενείς που δεν απαντούν στη θεραπεία με μεθοτρεξάτη ή αντι-TNF παράγοντες επιτυγχάνοντας ταχεία κλινική βελτίωση.

Τα ενθαρρυντικά αποτελέσματα από την χρήση του μορίου CTLA-4Ig στην κλινική πράξη οδήγησαν σε παραπέρα διερεύνηση του μηχανισμού δράσης. Φαίνεται ότι το συγκεκριμένο μονοκλωνικό οδηγεί σε αναστολή της παραγωγής των αντισωμάτων έναντι των κιτρουλιωμένων πρωτεϊνών (ACPAs) μέσω της τροποποίησης του μονοπατιού Syk της ενδοκυττάριας σηματοδότησης, το οποίο σχετίζεται με την επιβίωση και τον πολλαπλασιασμό των Β-λεμφοκυττάρων, καθώς ελαττώνει τη δραστηριότητα των $CD4^+$Th στα βλαστικά κέντρα.

Πέρα από τα συνδιεγερτικά μονοπάτια CD80/86 - CD28, CD80/86 - CTLA4 υπάρχουν και άλλες αλληλεπιδράσεις μεταξύ υποδοχέων της οικογένειας του CD28 και συνδιεγερτικών μορίων της οικογένειας του

CD80/86 που μπορούν να επάγουν ή να αναστείλουν την ενεργοποίηση των $CD4^+$Th και κατ' επέκταση να επηρρεάσουν την εξέλιξη της φλεγμονής στην ΡΑ. Στα επαγωγικά μονοπάτια ανήκει η σύνδεση του ICOS (Inducible Costimulator) στα ενεργοποιημένα $CD4^+$Th με τον ICOS-ligand στα ΑΠΚ, ενώ στα ανασταλτικά υπάγεται η αλληλεπίδραση του υποδοχέα PDI ($CD4^+$Th) με τα μόρια PDLI/PDL2 (ΑΠΚ, Β-λεμφοκύτταρα, ενδοθηλιακά κύτταρα).

Συνοψίζοντας, το σήμα από την αλληλεπίδραση $CD4^+$Th - ΑΠΚ μεταφέρεται ενδοκυτταρίως και μέσω σηματοδοτικών μονοπατιών, στα οποία προεξάρχοντα ρόλο παίζουν πρωτεΐνες με δράση τυροσινικής κινάσης, ρυθμίζει την έκφραση των γονιδίων διαφόρων κυτταροκινών που καθορίζουν την εξέλιξη της ανοσιακής απόκρισης.

Καταλήγοντας, γίνεται σαφές λοιπόν, ότι θεραπείες που στρέφονται προς την αναστολή του συνδιεγερτικού μονοπατιού είναι περισσότερο στοχευμένες και υπόσχονται ένα ικανοποιητικό θεραπευτικό αποτέλεσμα στην αντιμετώπιση της ΡΑ.

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PROGNOSIS OF NEUROBLASTOMA AND WILM'S TUMOR IN CHILDREN - AN UPDATE -

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INTRODUCTION: Malignant solid tumors in children exhibit special characteristics, which impose different management strategies than those in adults. Their rarity, their presentation and biologic behavior, the need for central catheter insertion for adjuvant therapy, the possible consequences of therapy in future fertility and the effort for less amputative interventions are crucial elements in the configuration of the management plan. Prognostic factors of paediatric malignant tumors, besides histopathology, the extend of the tumor, the presence of metastases and the response to therapy, are their genetic background, special biologic markers, the age of the child and the possibility of gene therapy implementation.

For the better understanding of *tumorigenesis* in children, some basic genetic terms have to be mentioned:

Proto-oncogenes, tumor suppressor genes and *mutator genes* play important role in the normal cell proliferation. Proto-oncogenes' products trigger cell proliferation, while the products of tumor suppressor genes inhibit cell proliferation. Mutator genes' products are mainly involved in the procedure of replication and repair of the DNA. Mutations regarding these three types of cells may result in the malignant transformation of a normal cell.

Telomerase enzyme is responsible for the restoration of the chromosomal final ends (telomeres). It is inactivated in most normal cells; on the contrary, it is found activated at all human cancers. Telomerase enzyme does not itself cause transformation, but it enables the uncontrolled proliferation of cancer cells. The degenerated cells have very short telomeres, which make them unable to multiply; the activation of telomerase at these cells elongates the short telomeres, stabilizes the chromosomes and enables cell proliferation.

The term *Loss of Heterozygosity (LOH)* refers to the tumor suppressor genes, which are located at both allelic chromosomes (homozygosity) and become inactivated or get lost, when an error at the DNA sequence occurs. They are alleles, so in order the production of tumor suppressor proteins to be blocked, these genes have to become inactivated at both allelic chromosomes, i.e. no normal allelic tumor suppressor gene to be found at any of the two chromosomes, even in heterozygosity (LOH - Loss of Heterozygosity).

The process of carcinogenesis leads to cancer cells, which carry DNA that may have point mutations, viral insertions, chromosomal or gene amplifications, deletions or rearrangements.

NEUROBLASTOMA- PROGNOSTIC FACTORS

Age. The younger the age, the better the prognosis. Congenital neonatal neuroblastoma has a very good prognosis.

Genetic background. The amplification (>10 times) of *MYCN* oncogene (2p;24) is a negative prognostic factor. Other chromosomal disorders, such as gains at the long arms of chromosomes 1 and 17 or deletions at the short arm of chromosome 1 and DNA polyploidy, are also related with poor neuroblastoma prognosis.

Stage. Taking into account the size of the tumor, its extend, the presence of lymph nodes and of metastases, the *International Neuroblastoma Staging System (INSS)* describes four stages of neuroblastoma. Stage IVS has special characteristics with considerably good prognosis depending on age.

Histopathology. *Shimada* classification system and its updated revision *International Neuroblastoma Pathology Classification (INPC)* combines histopathology (favorable, unfavorable), age and Mitotic Karryorrhexis Index (MKI).

Biologic markers. NSE, LDH, ferritin, glucoprotein MRP and B GL kinases have also been introduced as additional prognostic markers.

Response to therapy. The standard therapy scheme combines surgical excision of the tumor, adjuvant therapy plus radiation. The *DNA ploidy* is an independent prognostic factor for the response of the tumor to the therapy.

The International Neuroblastoma Risk Groups (INRG) based on the INSS stage, the age, the MYCN amplification status, DNA ploidy and INPC pathology describes four categories: the very low risk group with >85% 5-year survival, the low with 75-85%, the intermediate with 50-75% and the high risk group with <50% 5-year survival.

WILM'S TUMOR – PROGNOSTIC FACTORS

Stage. Staging includes the size, the extend of the tumor beyond the renal capsule, its extend in the renal vein or the vena cava, the presence of lymph nodes, of metastases and being bilateral. Stage I has 97% 5-year survival, stage II 86%, stage III 80%, stage IV 60% and the bilateral stage V has 82% 5-year survival.

Histopathology. It is based on the presence of blastemic, stromal or epithelial cells, cystic or solid elements, hemorrhagic or necrotic areas and the location (limited at one pole with definite demarcation line from the normal renal parenchyma). The favorable type refers to the 90% of the children with WT, whereas the unfavorable type (anaplastic) has poor prognosis.

Response to therapy. It is a very important factor in stage IV with lung metastases, in order radiation to be avoided; also in stage V (bilateral).

Genetic background. There is some correlation with prognosis, but not as strong as in neuroblastoma. The inactivation of the tumor suppressor gene TP53 at chromosome 17 (LOH) seems to play an important role.

CONCLUSIONS: Paediatric solid tumors, such as neuroblastoma and Wilm's tumor, are strongly associated with gene mutations and chromosomal alterations.

Recent research has shown that MIBG / adjuvant therapy, immunotherapy, anti-VGF, inhibitors of tyrosine kinase and telomerase may add to the overall prognosis of neuroblastoma.

Better understanding of the underlying DNA defects can lead to the implementation of new targeted therapies, such as gene therapy, which could ensure better prognosis and effective treatment in the near future.

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AUTOIMMUNE PANCREATITIS: A REVIEW OF CLINICAL PRESENTATION, DIAGNOSTIC CRITERIA AND TREATMENT

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Autoimmune pancreatitis (AP) is a relatively newly recognized disease with an extremely low prevalence. There are 2 types of AP. Type 1 is part of the IgG4-related syndrome with many extra-pancreatic manifestations such as sieladenitis, retroperitoneal fibrosis, interstitial nephritis, proximal biliary stenosis, sclerosing cholangitis as well as rheumatoid arthritis. Type 2 solely affects the pancreas despite the fact that 1/3 of the patients with AP2 may present with inflammatory bowel disease. The differential diagnosis between the two types is based on clinical, epidemiological, serological, radiological and most importantly on histological findings. The latter constitutes the gold standard for the definitive diagnosis of AP. More specifically, the outstanding histological feature in both types is a periductal lymphoplasmacytic infiltrate usually affecting some, or all of the medium sized ducts which is often accompanied by a collar-like periductal fibrosis, with narrowing of the affected duct, and by a perilobular fibrosis, occasionally of the storiform type. However, the diagnostic histological finding of a biopsy specimen for AP2 is the Granulocytic Epithelial Lesion (GEL) and the absence or scant (<10 cells/HPF) IgG4 positive staining plasma cells in the inflamed pancreatic tissue. Due to the confusion pertaining to the diagnosis of API, new criteria have been recently proposed (International Consensus Diagnostic Criteria-ICDC) for the clinical assessment of the patients. In order to reduce the number of unnecessary pancreatectomies, it is also crucial to differentiate pancreatic cancer from AP as they both present in the majority of the cases with obstructive jaundice, weight loss and pancreatic mass in the head of the pancreas. Although spontaneous resolution may occur in 30% of the cases of AP, use of oral prednisolone is still the initial treatment followed by an assessment of remission in 2 weeks based on a marked improvement in pancreatic duct narrowing and a reduction in size of the pancreatic mass. In case of relapse, which is more common among patients with a definitive diagnosis of API, oral prednisolone is the choice of treatment either co-administered with azathioprine or not.

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ΑΝΑΡΤΗΜΕΝΕΣ ΑΝΑΚΟΙΝΩΣΕΙΣ (E-POSTERS)

LATE BREAKING ABSTRACTS

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Ο ΡΟΛΟΣ ΤΗΣ ΙΝΤΕΡΛΕΥΚΙΝΗΣ-17 ΩΣ ΒΙΟΔΕΙΚΤΗ ΣΤΗΝ ΠΑΡΑΚΟΛΟΥΘΗΣΗ ΤΗΣ ΡΕΥΜΑΤΟΕΙΔΟΥΣ ΑΡΘΡΙΤΙΔΑΣ

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ΕΙΣΑΓΩΓΗ: Η ρευματοειδής αρθρίτιδα είναι μια χρόνια φλεγμονώδης, αυτοάνοση και εξελικτική νόσος, που προσβάλλει κυρίως τις αρθρώσεις και αρκετά συχνά διάφορα άλλα όργανα. Ο επιπολασμός της νόσου αγγίζει το 0,5-1% των ενηλίκων στον ανεπτυγμένο κόσμο. Η αιτιοπαθογένεια της νόσου παραμένει αδιευκρίνιστη, ενώ εμπλέκονται γενετικοί, περιβαλλοντικοί και κυρίως ανοσολογικοί μηχανισμοί με την συμβολή προ- και φλεγμονωδών κυτταροκινών.

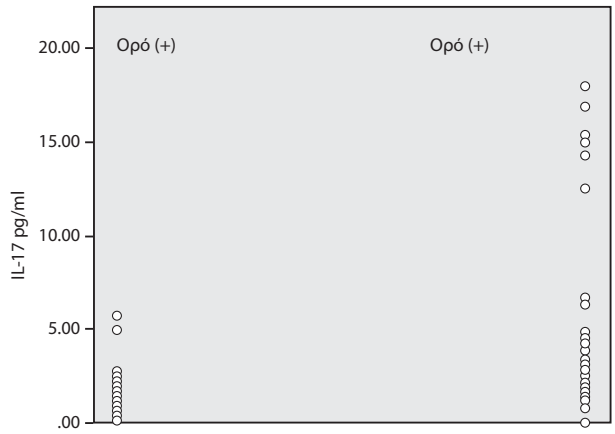
Η ρευματοειδής αρθρίτιδα χαρακτηρίζεται από υμενίτιδα, όπου προεξάρχει η κυτταρικού τύπου υπερευαισθησία. Πρόσφατα, άρχισε να εξετάζεται ο ρόλος των Th-17 κύτταρων και της ιντερλευκίνης 17 (IL-17) που συνθέτουν. Μελέτες δείχνουν ότι τα κύτταρα αυτά διαδραματίζουν σημαντικό ρόλο στην παθογένεση της νόσου επάγοντας τη φλεγμονή που οδηγεί στη καταστροφή των οστών. Η μελέτη της φλεγμονώδους κυτταροκίνης IL-17 έδειξε, ότι η συγκεκριμένη ιντερλευκίνη σχετίζεται με την υποτροπή ή την επαγωγή ύφεσης στη ρευματοειδή αρθρίτιδα και ότι αντι-IL-17 θεραπείες μπορεί να έχουν ευεργετικά αποτελέσματα. Στην παρούσα ερευνητική εργασία αξιολογήθηκαν τα επίπεδα IL-17 στον ορό ασθενών με ρευματοειδή αρθρίτιδα, με σκοπό να συσχετιστούν με κλινικές παραμέτρους και εργαστηριακούς δείκτες, ώστε να διευκρινιστεί ο ρόλος της κυτταροκίνης αυτής ως πιθανού βιοδείκτη στην πορεία της νόσου.

ΥΛΙΚΟ – ΜΕΘΟΔΟΣ: Στην παρούσα μελέτη, συμπεριλήφθηκαν 56 ασθενείς με ρευματοειδή αρθρίτιδα σε διάφορα στάδια ενεργότητας νόσου, 10 άνδρες και 46 γυναίκες, ηλικίας 32 έως 80 ετών (μέσος όρος 64 ± 11,35 έτη), με μέση διάρκεια νόσου 13 έτη (0,5 - 50 έτη). Στους ασθενείς μετρήθηκαν τα επίπεδα IL-17 στον ορό. Ο προσδιορισμός έγινε με την ανοσοενζυμική μέθοδο ELISA (Human IL-17A Platinum Sandwich Eliza). Παράλληλα, εκτιμήθηκαν οι κλινικοί δείκτες DAS-28 (disease activity score 28 – κλινικός δείκτης που καταμετρά ενεργότητα σε 28 προκαθορισμένες αρθρώσεις), VAS (visual analogue scale – οπτική κλίμακα αξιολόγησης της νόσου από τον ασθενή), HAQ (health assessment questionnaire – δείκτες λειτουργικής ικανότητας) και οι εργαστηριακοί δείκτες ΤΚΕ, CRP, RFs, αντι-CCPs αντισώματα που χρησιμοποιούνται για τη διάγνωση και την παρακολούθηση της νόσου. Δεν κρίθηκε σκόπιμο να αναλύσουμε ως προς είδος θεραπείας, καθώς δεν υπήρχε ομοιογένεια ως προς αυτό. Έγινε συσχέτιση των επιπέδων της IL-17 με τις παραπάνω παραμέτρους με γραμμική παλινδρόμηση (IBM SPSS STATISTICS version 22).

ΑΠΟΤΕΛΕΣΜΑΤΑ: Από τη στατιστική ανάλυση προέκυψε ότι η IL-17 του ορού αυξάνεται γραμμικά με τον DAS-28 (β= 1,415, p=0,005), τον HAQ (β=1,468, p=0,024), την ΤΚΕ (β=0,103, p=0,001), τον RF (β=0,023, p=0,000) και τα anti-CCPs (β=0,03, p=0,000). Αντιθέτως, δεν παρουσιάζει σημαντική συσχέτιση με το δείκτη VAS (β=0,034, p=0,249), και τη CRP (β=0,020, p=0,593).

Πίνακας Ι. Αύξηση της IL-17 του ορού σε σχέση με κλινικούς και εργαστηριακούς δείκτες.

Δείκτης	Συντελεστής β	CI95%	p
DAS-28	1,415	0,434-2,395	0,005
VAS	0,034	-0,024-0,092	0,249
HAQ	1,468	0,200-2,735	0,024
TKE	0,103	0,043-0,164	0,001
CRP	0,020	-0,054-0,093	0,593
RFs	0,023	0,014-0,033	0,000
anti-CCPs	0,030	0,014-0,045	0,000



Γράφημα 1. *Επίπεδα IL-17 σε οροαρνητικούς (1) και οροθετικούς (2) ασθενείς με ρευματοειδή αρθρίτιδα.*

Η IL-17 του ορού είναι σημαντικά αυξημένη στους οροθετικούς σε σχέση με τους οροαρνητικούς ασθενείς (μέση διαφορά 3,629 pg/ml, CI 95% 1,360-5,898, p=0,002).

ΣΥΜΠΕΡΑΣΜΑ: Από τα αποτελέσματα μας προκύπτει πως η IL-17 αυξάνεται σημαντικά στον ορό οροθετικών ασθενών με ενεργό νόσο (υψηλό DAS-28) και με επηρεασμένη λειτουργική ικανότητα (HAQ). Αντιθέτως, τα επίπεδα είναι χαμηλότερα σε οροαρνητικούς ασθενείς με χαμηλή ενεργότητα νόσου (χαμηλό DAS-28) και ικανοποιητική λειτουργική ικανότητα (χαμηλό HAQ), δηλαδή σε ασθενείς που είναι γνωστό ότι παρουσιάζουν καλύτερη πρόγνωση. Η IL-17 λοιπόν, θα μπορούσε να λειτουργήσει ως βιοδείκτης στην παρακολούθηση της πορείας της ρευματοειδούς αρθρίτιδας. Όμως, απαιτείται να μελετηθούν τα επίπεδα της IL-17 σε μεγαλύτερο πληθυσμό ασθενών.

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ΥΠΟΛΟΓΙΣΜΟΣ ΤΩΝ ΑΠΟΤΕΛΕΣΜΑΤΩΝ ΣΕ (ΡΑΔΙΟ)ΑΝΟΣΟΛΟΓΙΚΕΣ ΕΞΕΤΑΣΕΙΣ

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Η εργασία δημοσιεύεται ως πλήρες κείμενο (σελίδα 9).

ΟΔΗΓΙΕΣ ΓΙΑ ΤΟΥΣ ΣΥΓΓΡΑΦΕΙΣ

Το περιοδικό «Ανοσία» εκδίδεται από την Ελληνική Εταιρεία Ανοσολογίας και αποτελεί το μέσο προώθησης της ανοσολογίας στους χώρους διεξαγωγής ιατρικής έρευνας και κλινικής πράξης. Στο περιοδικό δημοσιεύονται άρθρα σύνταξης, ανασκοπικά άρθρα, ερευνητικές και άλλες πρωτότυπες εργασίες, ενδιαφέρουσες περιπτώσεις και γράμματα από και προς τη σύνταξη.

Υποβολή άρθρων: Τα άρθρα αποστέλλονται στον εκδότη στη διεύθυνση:

Α. Σαραντόπουλος
Για το περιοδικό ΑΝΟΣΙΑ
Τμήμα Κλινικής Ανοσολογίας
Β΄ Παθολογική Κλινική ΑΠΘ
Κωνσταντινουπόλεως 49,
546 42 Ιπποκράτειο Γ.Ν.Π.Θ.
Θεσσαλονίκη

Για κάθε τύπο άρθρου ισχύουν ιδιαίτερες οδηγίες:

1. Άρθρα σύνταξης: Συνοπτικά άρθρα που δεν υπερβαίνουν τις 2 σελίδες. Η έκτασή τους δεν πρέπει να υπερβαίνει τις 500 λέξεις.
2. Άρθρα ανασκοπικά: Πρόκειται για σύνθετη παρουσίαση ενός θέματος που περιλαμβάνει την εξέλιξή του μέχρι σήμερα αλλά κυρίως τις νεότερες απόψεις και προοπτικές. Το μέγεθος του άρθρου δεν πρέπει να υπερβαίνει τις 4.000 λέξεις.
3. Ερευνητικές, πρωτότυπες εργασίες: Έχουν κλινικό ή εργαστηριακό χαρακτήρα ή αποτελούν προϊόν βασικής έρευνας, ενώ η δομή τους πρέπει να περιλαμβάνει περίληψη, περιγραφή υλικού και μεθοδολογίας, αποτελέσματα και συζήτηση. Δεν πρέπει να υπερβαίνουν τις 3.500-4.000 λέξεις.
4. Ενδιαφέρουσες περιπτώσεις: Παρουσίαση περιστατικών σπάνιων είτε ως προς την κλινικοεργαστηριακή τους πορεία είτε ως προς τη θεραπευτική τους αντιμετώπιση και εξέλιξη. Τα άρθρα πρέπει να είναι 1.000-1.500 λέξεων.
5. Γράμματα προς τη σύνταξη: Περιλαμβάνουν ανακοινώσεις πρόδρομων αποτελεσμάτων, είτε σχόλια που αφορούν δημοσιευμένα στο περιοδικό άρθρα. Δεν θα πρέπει να υπερβαίνουν τις 500 λέξεις.

Σύνταξη χειρογράφων: Τα άρθρα που αποστέλλονται στο περιοδικό πρέπει να είναι γραμμένα στη νεοελληνική δημοτική. Υποβάλλονται σε σελίδες τύπου Α4, με διπλό διάστημα και περιθώρια, ενώ οι γραμματοσειρές που πρέπει να χρησιμοποιούνται είναι οι Times New Roman και Arial.

Αποτελούν ξεχωριστές ενότητες και πρέπει να υποβάλλονται σε ιδιαίτερη σελίδα:

Α) Ο τίτλος της εργασίας με τα ονόματα των συγγραφέων, το ίδρυμα από το οποίο προέρχονται και τη διεύθυνση του συγγραφέα για αλληλογραφία.

Β) Η περίληψη της εργασίας (με την ανάλογη δομή), η οποία δεν πρέπει να υπερβαίνει τις 200 λέξεις, μαζί με 3-5 λέξεις-κλειδιά.

Γ) Το κείμενο της εργασίας. Στις ερευνητικές εργασίες ακολουθείται η σειρά: εισαγωγή, υλικό και μέθοδοι, αποτελέσματα και συζήτηση. Εάν πρόκειται για κλινική μελέτη, τότε πρέπει να αναφέρεται ότι πραγματοποιήθηκε σύμφωνα με τη διακήρυξη του Ελσίνκι. Οι φαρμακευτικές ουσίες αναφέρονται με την κοινόχρηστη και όχι την εμπορική ονομασία τους.

Δ) Ο τίτλος της εργασίας με τα ονόματα των συγγραφέων, τα αντίστοιχα ιδρύματα απ' όπου προέρχονται, το κείμενο της περίληψης και τις λέξεις-κλειδιά στην Αγγλική.

Ε) Οι βιβλιογραφικές παραπομπές.

ΣΤ) Οι υπότιτλοι των εικόνων και οι επεξηγήσεις των σχημάτων και πινάκων. Κάθε υπότιτλος παρατίθεται σε ξεχωριστή σελίδα.

Ζ) Οι πίνακες, σχήματα και εικόνες που δυνατό να συνοδεύουν το κείμενο και πρέπει να παρατίθενται σε ξεχωριστές σελίδες. Οι εικόνες πρέπει να έχουν ανάλυση 300 dpi τουλάχιστον.

Για την περίπτωση εκτύπωσης έγχρωμων εικόνων, ο συγγραφέας θα ενημερώνεται από τη Συντακτική Επιτροπή για τη διαφορά κόστους, την οποία και θα αναλαμβάνει ο ίδιος να καλύψει.

Βιβλιογραφικές παραπομπές: Το περιοδικό «Ανοσία» ακολουθεί το σύστημα Vancouver σύμφωνα με το οποίο οι παραπομπές εμφανίζονται στο κείμενο με μορφή αριθμών. Εφόσον οι συγγραφείς είναι περισσότεροι από έξι, αναφέρονται οι 3 πρώτοι και ακολου-

θεί η σύντμηση: και συν. ή et al. Οι συντμήσεις των περιοδικών παρατίθενται σύμφωνα με το Abridged Index Medicus π.χ.

Μπούρα Π. Ανοσιακή απόκριση. Στο: Τομέας Παθολογίας, Ιατρική Σχολή ΑΠΘ, Εσωτερική Παθολογία, Θεσσαλονίκη, University Studio Press, 2004: 49-53.

Boura P, Papadopoulos S, Tselios K, et al. Intracerebral hemorrhage in a patient with SLE and catastrophic antiphospholipid syndrome (CAPS): report of a case. Clin Rheumatol 2005 Aug; 24(4): 420-4.

Όλα τα παραπάνω συγκροτούν το συνολικό κείμενο υποβολής και πρέπει αυτό να αποστέλλεται σε τρία αντίτυπα στον εκδότη του περιοδικού, μαζί με μια δισκέτα όπου θα περιέχεται η εργασία σε ηλεκτρονική μορφή.

Κάθε υποβολή πρέπει να συνοδεύεται από ενυπόγραφη επιστολή του πρώτου συγγραφέα όπου θα δηλώνεται ότι η εργασία δεν βρίσκεται σε διαδικασία κρίσης και δεν έχει δημοσιευθεί από οποιοδήποτε άλλο περιοδικό και ότι όλοι οι συγγραφείς συμφωνούν στην πιθανή δημοσίευσή της.

Εφόσον η εργασία είναι τυπικά ολοκληρωμένη σύμφωνα με τις παραπάνω οδηγίες προωθείται από την επιτροπή επιμέλειας σύνταξης σε 2 μέλη της συμβουλευτικής επιτροπής. Οι κριτές κάνουν δεκτή ή απορρίπτουν την εργασία, ενώ διατυπώνουν τις παρατηρήσεις τους οι οποίες επιστρέφονται μαζί με την εργασία στους συγγραφείς. Στο στάδιο της τελικής φάσης της εκτύπωσης αποστέλλεται στους συγγραφείς το τελικό δοκίμιο το οποίο επιδέχεται πλέον μόνο ορθογραφικές διορθώσεις. Στο σημείο αυτό γίνεται και η παραγγελία των ανατύπων από τους συγγραφείς. Εργασίες που δημοσιεύονται στο περιοδικό «Ανοσία» αποτελούν πνευματική του ιδιοκτησία και η αναδημοσίευση μέρους ή ολόκληρου του κειμένου απαιτεί την έγγραφη συγκατάθεση του εκδότη.