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Editorial
Άρθρο σύνταξης

The importance of the patients deemed not guilty by reason of insanity for the psychiatric reform

Psychiatriki 2016, 27:165–168

According to the Greek Penal Law if someone "because of a morbid disturbance of his mental functioning" (article 34) is acquitted of a crime or misdemeanour that the law punishes with more than 6 months imprisonment, then the court orders that this individual should be kept in a public psychiatric institution if the court reaches the conclusion that this person poses a threat to public safety.[1] Individuals who have broken the law and deemed "not guilty by reason of insanity" are treated in psychiatric units of Psychiatric Hospitals according to the article 69 of the Penal Code. In Athens, in the Psychiatric Hospital of Athens and the Dromokaiteion Psychiatric Hospital, and in Thessaloniki in the Unit for "Not guilty by reason of insanity (NGRI)".

The person who is deemed not guilty by reason of insanity following a crime is facing double stigmatisation and marginalisation from both the legal and the health system. He/she is usually treated initially with fear and later since there is no therapeutic aim but only the court instruction for "guardianship", with indifference.

The patient who is committed by the courts in a psychiatric unit for being "NGRI" is facing a unique legal and psychiatric status.[2] In this respect he/she is disadvantaged when compared to either convicted criminals or psychiatric inpatients. If the patient was not found "NGRI" (ie innocent as far as sentencing is concerned) he would have been punished with loss of liberty for a certain (specific) amount of time, and like all individuals convicted in court he/she would have the right to appeal and reduce his/her sentence in a higher court and maybe released from prison earlier for good behaviour etc. In this respect the individual found to be "NGRI" is disadvantaged when compared to a convicted felon since he/she is kept for an undefined period of time. Additionally, he/she will be allowed to leave the psychiatric unit following a subjective assessment of a judge with no psychiatric knowledge who will decide that this certain individual has "ceased to be dangerous". These problems are accentuated by the difficulties that the Greek justice system is facing.

On the other side, from the psychiatric point of view, the "NGRI" patient who is an inpatient is not receiving the holistic, (bio psycho social) treatment and assessment of needs he/she requires. The psychiatric team looking after him, once the acute symptomatology is controlled is just getting used to a patient who will not be discharged in the immediate future. These patients form the "new chronic asylum psychiatric inpatients" for whom the treating psychiatrists are not allowed to discharge back into the community whilst it is unclear whether they can be transferred to supported rehabilitation units. It is a medical but also legal paradox to assign to contemporary psychiatric units aiming mainly to treat patients in the community to "keep and guard" inpatients whilst these psychiatric units should focus on care and rehabilitation of the patients (including the "NGRIs").[3] Keeping patients like these in psychiatric units creates problems in the functioning of the units. These patients are "kept" in acute beds for long periods of time (5 to 6 years minimum) with patients treated voluntarily or against their will and cannot be discharged without a court's decision. The problems are obvious if one realises that the average time of hospitalisation is not exceeding 2 months for the vast majority of psychiatric patients. With the prolonged stay patients of the "article 69" (NGRIs) they not only burden the already limited resources (there is an established lack of psychiatric beds nationwide) but also this prolonged hospitalisation increases their stigmatisation and marginalisation. Thus the prolonged hospitalisation for "safety" reasons according to the court decision leads to the absence of a therapeutic aim other than maintaining the patient on the ward.

Greece has agreed that there is an urgent need in developing community psychiatry services and closure/transformation of the big psychiatric hospitals (asylums). It is impossible to close hospitals where "NGRIs" are kept. The decision to move them into the community is not a medical-psychiatric but a legal one. In this respect it is imperative to establish a Forensic Psychiatric Unit for these patients.

In our country as the "Psychargos" external evaluation highlighted, there are great gaps in the provision of Forensic psychiatric services.[3] It must be emphasised that these gaps affect negatively psychiatric reform and social reintegration not only for the forensic psychiatric patients but for the whole of mentally ill individuals. Given that forensic Psychiatric services are developed in Athens and Thessaloniki and that training in Forensic Psychiatry has moved forward, it is imperative that the state should build upon the existing knowledge and experience and create specialist forensic units aiming to treat and rehabilitate this special and important group of patients.[4] Only when the patients found "not guilty by reasons of insanity" have their own (safe for the society and them) therapeutic and rehabilitative services the aim of de-institutionalisation will be visible and realistic to implement.

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Άρθρο σύνταξης
Editorial

Η σημασία των «ακαταλόγιστων» για την ψυχιατρική μεταρρύθμιση

Ψυχιατρική 2016, 27:165–168

Σύμφωνα με τον Ελληνικό Ποινικό Κώδικα (ΠΚ), αν κάποιος, «λόγω νοσηρής διατάραξης των πνευματικών λειτουργιών του» (άρθρο 34) απαλλάχθηκε από την ποινή ή τη δίωξη για κακούργημα ή πλημμέλημα, για το οποίο ο νόμος τιμωρεί με ποινή ανώτερη από έξι μήνες, το δικαστήριο διατάσσει τη φύλαξή του σε δημόσιο θεραπευτικό κατάστημα εφόσον κρίνει ότι είναι επικίνδυνος για τη δημόσια ασφάλεια.[1] Οι παραβάτες που έχουν κριθεί ακαταλόγιστοι νοσηλεύονται σε ψυχιατρικά τμήματα των Ψυχιατρικών Νοσοκομείων της Αθήνας, ΨΝΑ και Δρομοκαΐτειο για «φύλαξη» σύμφωνα με το Άρθρο 69 του Π.Κ. Στη Θεσσαλονίκη νοσηλεύονται στο Τμήμα Ψυχιατροδικαστικής (Ακαταλογίστων).

Το άτομο με ψυχική διαταραχή που έχει κριθεί ακαταλόγιστο για μια εγκληματική πράξη αντιμετωπίζει διπλό στιγματισμό και περιθωριοποίηση τόσο από τον δικαστή όσο και από το ψυχιατρικό θεραπευτικό πλαίσιο, που τον αντιμετωπίζει αρχικά με φόβο και στη συνέχεια μην έχοντας θεραπευτικό στόχο πέραν της «φύλαξης» με αδιαφορία. Υποβάλλεται σε ένα «μοναδικό» νομικό-ψυχιατρικό καθεστώς το οποίο από τη μία διαφέρει τόσο από το καθεστώς του απλού παραβάτη όσο και από το καθεστώς ενός νοσηλευόμενου σε ψυχιατρική μονάδα, και από την άλλη μειονεκτεί έναντι αυτών.[2] Ο εν λόγω ασθενής υστερεί συγκρινόμενος με κάποιον καταδικασμένο αλλά και με κάποιον που νοσηλεύεται σε ψυχιατρική κλινική. Αν ο ασθενής αυτός δεν είχε κριθεί ακαταλόγιστος (άρα και αθώος αναφορικά με την ποινή που πρέπει να του επιβληθεί) θα είχε τιμωρηθεί σύμφωνα με τον Ποινικό Κώδικα για συγκεκριμένο χρόνο ποινής, και –όπως όλοι όσοι/ες έχουν καταδικασθεί– θα είχε το δικαίωμα να ασκήσει έφεση και να μειώσει την ποινή του σε ανώτερο δικαστήριο, και βέβαια να τύχει των ευεργετικών διατάξεων του νόμου για πρόωρη αποφυλάκιση κ.λπ. Υπό αυτήν την έννοια στερείται και μειονεκτεί του ποινικού κρατούμενου, αρχικά στον χρονικό προσδιορισμό της ποινής, εφόσον ο δεύτερος υποβάλλεται σε μια αορίστου χρόνου «φύλαξη». Παράλληλα, η έξοδός του από το Ψυχιατρικό τμήμα βασίζεται στα υποκειμενικά κριτήρια του εκάστοτε δικαστή που κρίνει αν «έχει παύσει η επικινδυνότητα». Η κατάσταση αυτή επιδεινώνεται από τη μεγάλη καθυστέρηση στην εκδίκαση υποθέσεων των ελληνικών δικαστηρίων.

Από ψυχιατρικής πλευράς, ο νοσηλευόμενος ακαταλόγιστος ασθενής δεν λαμβάνει την απαραίτητη ολιστική (βιοψυχοκοινωνική) φροντίδα, και το προσωπικό της μονάδας –εφόσον ελεγχθεί η οξεία συμπτωματολογία και η συμπεριφορά– εξοικειώνεται με έναν ασθενή ο οποίος δεν πρόκειται να λάβει εξιτήριο. Οι ασθενείς αυτοί αποτελούν τους «νέους χρόνιους-ασυλικούς» ψυχιατρικά νοσηλευόμενους, στους οποίους οι θεράποντες ψυχίατροι δεν επιτρέπεται να δώσουν εξιτήριο, ενώ είναι ασαφές εάν δύνανται να μετακινηθούν σε ξενώνες αποκατάστασης. Αποτελεί «ιατρικό αλλά και νομικό παράδοξο»[3] να ανατίθεται η «φύλαξη» σε σύγχρονες ψυχιατρικές μονάδες, που κατά κύριο λόγο λειτουργούν βάσει των αρχών της αποασυλοποίησης, ενώ σαφώς στις υποχρεώσεις των Ψυχιατρικών Νοσοκομείων και Κλινικών εμπίπτουν η ψυχιατρική φροντίδα και η αποκατάσταση του ασθενούς (άρα και του «ακαταλογίστου) και όχι η φύλαξη και ο σωφρονισμός του.

Η παραμονή των ασθενών αυτών στα Ψυχιατρικά Τμήματα δημιουργεί προβλήματα στη λειτουργία τους, καθώς καταλαμβάνουν κλίνες «οξέων» περιστατικών για μεγάλο χρονικό διάστημα (5–6 χρόνια τουλάχιστον) και δεν μπορούν να λάβουν εξιτήριο αν δεν συναινέσει η δικαστική αρχή. Τα προβλήματα γίνονται άμεσα εμφανή, αν γίνει αντιληπτό ότι ο μέσος όρος νοσηλείας στα Ψυχιατρική τμήματα νοσηλείας δεν υπερβαίνει τους 2 μήνες στη συντριπτική πλειονότητα των ψυχικά πασχόντων. Με τη μακροχρόνια παραμονή τους, οι ασθενείς του «άρθρου 69» αφενός επιβαρύνουν τις ήδη περιορισμένες δυνατότητες (λόγω σημαντικής έλλειψης κλινών νοσηλείας στα ψυχιατρικά νοσοκομεία/τμήματα) ενδονοσοκομειακής θεραπείας, και αφετέρου η παραμονή αυτή αυξάνει τον στιγματισμό και την περιθωριοποίησή τους.

Η μακροχρόνια λοιπόν νοσηλεία «για φύλαξη» σύμφωνα με τη δικαστική απόφαση οδηγεί και στην απουσία θεραπευτικού στόχου πέραν της παραμονής στο τμήμα.

Η χώρα μας έχει συμφωνήσει στην ανάγκη ανάπτυξης της κοινοτικής ψυχιατρικής και στο κλείσιμο/μετασχηματισμό των μεγάλων ψυχιατρικών νοσοκομείων. Δεν είναι δυνατόν να κλείσουν νοσοκομεία στα οποία νοσηλεύονται ψυχικά πάσχοντες που έχουν κριθεί ακαταλόγιστοι. Η απόφαση για τη μεταφορά τους στην κοινότητα δεν είναι ιατρική/ψυχιατρική αλλά δικαστική. Είναι λοιπόν απαραίτητο να δημιουργηθεί ένα ειδικό τμήμα στην Αθήνα για τα άτομα αυτά.

Στη χώρα μας όπως τόνισε και η αξιολόγηση του «Ψυχαργώς», υπάρχουν πολύ μεγάλα κενά στην παροχή Ψυχιατροδικαστικών υπηρεσιών.[3] Τα κενά αυτά πρέπει να γίνει αντιληπτό ότι επιβραδύνουν την ψυχιατρική μεταρρύθμιση και την κοινωνική επανένταξη όχι μόνον των Ψυχιατροδικαστικών ασθενών, αλλά όλων των ψυχικά πασχόντων. Δεδομένου ότι Ψυχιατροδικαστικές υπηρεσίες έχουν πλέον αναπτυχθεί στην Αθήνα και στη Θεσσαλονίκη και ότι η εκπαίδευση στην Ψυχιατροδικαστική έχει προχωρήσει, είναι απαραίτητο η πολιτεία να στηριχθεί στην υπάρχουσα τεχνογνωσία και πείρα και να προχωρήσει στην ανάπτυξη αμιγώς Ψυχιατροδικαστικών τμημάτων αυξημένης φροντίδας με στόχο τη θεραπεία και κοινωνική επανένταξη της ειδικής και σημαντικής αυτής ομάδας ασθενών.[4] Μόνο όταν οι «ακαταλόγιστοι» αποκτήσουν το δικό τους ασφαλές (για την κοινωνία και τους ιδίους) θεραπευτικό/αποκαταστασιακό πλαίσιο θα είναι ορατός ο στόχος της αποασυλοποίησης.

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Research article
Ερευνητική εργασία

Maternal screening for early postnatal vulnerability

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Research has highlighted the wide impact of maternal mental health problems during and beyond the postpartum period and the public health role of community health professionals in early detection of women who may be at risk. This paper aims to describe, explore and test an a priori hypothesised conceptual model of postnatal experience, identifying the relationships between postnatal mental vulnerability and postnatal adjustment to maternal roles and attitudes, marital/partner-relationship and sense of coherence. Three validated self-report questionnaires (WAST, MAMA, SOC) measuring the variables of the encompassing framework and EPDS were administered in random order. The conceptual models were tested using the software IBM SPSS Statistics and LISREL and the tests performed were: Student's t-test, chi-square tests, Explanatory factor analysis using a Varimax rotation Principal Components Method, Confirmatory analysis –known as structural equation modelling– of principal components. Psychometric scores indicate high correlation between WAST, MAMA, SOC and EPDS. An exploratory factor analysis confirmed the role of SOC, specific MAMA subscales (maternal roles and attitudes, body image, sex, breasts, nausea) and WAST (relationship tension and emotional and physical abuse) subscales (KMO measure of sampling adequacy=0.735 and Bartlett's test of sphericity=184,786, df=36, p<0.0005). The latent variables confirmed with SEM were marital relationship, maternity experience and self-efficacy (Chi-square=28.45, df=24, P-value=0.24, RMSEA=0.046

p<0.05). Marital Relationship (Factor I: Eigenvalue=3.066) concerning lack of or disappointment with partner support, poor marital relationship and emotional/physical abuse has been associated with high levels of postpartum anxiety and depression. Maternity Experience (Factor II: Eigenvalue=1.280) representing postnatal roles and attitudes towards their infant can be as useful as mood changes for evaluation of mothers. Self-Efficacy (Factor III: Eigen- value=3.144) and especially attitudes regarding body image, sex and coping resources and options of dealing with the stressor, has been demonstrated that serve as a mediator or buffer for psychological distress. The results of this study have implications for the prevention and intervention of postnatal adjustment difficulties both of which need to be intensified in order to minimise perinatal mental vulnerability.

Key words: Depression symptoms, postpartum, abuse, maternity experience, self-efficacy.

Introduction

A considerable number of women experience mental health symptoms after childbirth.[1,2] During the early postpartum period the incidence of depressive symptoms affects from 8.5–84%[3–6] of women, and the wide variation in incidence could be justified due to the timing of identification of symptoms and how this was undertaken. Depression has been determined to be a major global public health concern, contributing to poor physical and mental health in affected women.[1,7] However, early postpartum depression symptoms often go unrecognized with several consequences for the woman, the newborn and the family.[8–11]

To this end, efforts to meet these health needs are considered, as a potential benchmark of establishing an effective primary care system.[3,12] Recent studies attempted to identify psychosocial factors that may contribute to depression symptoms during the early postpartum period.[3,7,11–14] In order to explore the determinants of postpartum depressive symptomatology a comprehensive conceptual framework was constructed.

The first level of the framework concerns the postnatal adjustment to maternal roles and attitudes (MAMA). The perception of psychosocial adaptation during the postpartum period and its effects on women requires consideration due to the many psychosocial risk factors that may affect a woman's experience.[15–16] Women who appear to adjust with much difficulty to their new maternal roles may have a specific postnatal vulnerability to mental health problems.[17] Postnatal roles and attitudes regarding body image, sex, somatic symptoms, marital relationship and attitude towards their infant can be as useful as mood changes for evaluation of women.[15,18,19]

The second level of the framework represents the attachment in the marital/partner-relationship (WAST). These concepts can determine, in part, "the quality" of attachment in the partner-relationship –the individual's typical pattern of relating to their partner– was included in the framework to represent the link between the couple's relationship and symptoms of depression. The partner is usually highly valued as a source of support for childbearing women.[3,13] In addition, previous studies have revealed that support from a partner facilitated women to adapt to maternal roles during postpartum period, for example when making decisions to continue to breastfeed.[20,21] Lack of or disappointment with partner support has been associated with high levels of postpartum anxiety and depression.[3,22] Poor marital relationship and emotional/physical abuse[13,23–26] has been consistently reported as an important predictor of postpartum depression. Women who lack partner support and women who experience psychological abuse are more likely to

sustain a negative impact on their mental health after birth.[13,27,28]

A third level of the framework concerns Sense of coherence (SOC). This may be the most direct expression of the self efficacy, self-concept as a personal force. It refers to the perception or experience of oneself as a causal agent in the family setting. Sense of coherence is an important factor in various health related behaviours, such as overcoming phobias and anxieties, eating disorders and alcohol or smoking addictions.[29–34] It is also congruent with emphasis on self-reliance, mastery and individualism. Sense of coherence describes the confidence the woman feels about performing a particular activity, including confidence in overcoming barriers to performing maternal attitudes/roles and it is the most important prerequisite for behavior change because it affects how much effort could be invested in the specific task and what level of performance is attained.[29–34] Stressful events are construed as person-environment transactions around two critical processes, namely primary and secondary appraisal. Primary or cognitive appraisal is a person's evaluation of the significance of a stressor. For example, the postnatal period is likely to be perceived as stressful period by those for whom parenthood is viewed as a central life goal, whereas those for whom parenthood is not viewed this way, the postnatal period might be appraised as a not particularly stressful time. These individuals might be less susceptible to psychological distress. Secondary appraisal is an assessment of the person's coping resources and options of dealing with the stressor, for example, parents might seek support from postnatal groups or talk about their emotions with their friends or relatives to deal with their difficulties. It has been suggested that coping may serve as a mediator or buffer for psychological distress.[3]

Consequently, the general aim of this exploratory study was to describe, explore and test a self-constructed conceptual framework to help understand the relative impact of postnatal adjustment to maternal roles and attitudes (MAMA), marital/partner relationship (WAST) and sense of coherence (SOC) on levels of depressive symptoms during early postpartum period.

Subjects and methods

Study setting, sampling and target population

The translated, culturally adapted versions of the EPDS, WAST, MAMA and SOC were administered throughout the postnatal units of the four Hospitals. Women who gave birth from June 2009 to August 2009 in these hospitals were eligible for participation, provided they were: (1) 18 to 45 years old (2) remained at the unit for their postnatal stay (3) able to separate themselves from individuals who accompanied them (4) fluency in spoken and written Greek language (5) who were well and (6) able to provide informed written consent. Women were excluded if they had experienced an episode of depression within the previous 2 years or if they had received pharmacological or psychotherapeutic treatments for depression that lasted 3 continuous months (minimum treatment of once a week). The study flow diagram is shown in the figure 1.

Data collection and instruments

In addition to standard socio-demographic questions, the mothers completed the EPDS, WAST, MAMA and SOC questionnaires in the presence of a midwife during their stay at the postnatal ward with alternative order of completion of the four questionnaires. There was no reference to the terms "abuse" or "violence" until the study subject was in a private room, where the study aims were explained and informed consent was obtained.

Edinburgh Postnatal Depression Scale (EPDS)[35]

EPDS, a 10 item self report scale, each item scoring 0–3, depending on the severity or duration of each symptom as experienced in the previous 7 days. The Greek version of the EPDS showed high internal consistency (Chronbach's alpha=0.804 and Guttman split-half coefficient 0.742) and was significantly correlated (Pearson r=0.66, p<0.0005) to the validated Greek version of BDI-II (Beck Depression Inventory II).[36] A threshold score of 8/9 fitted the

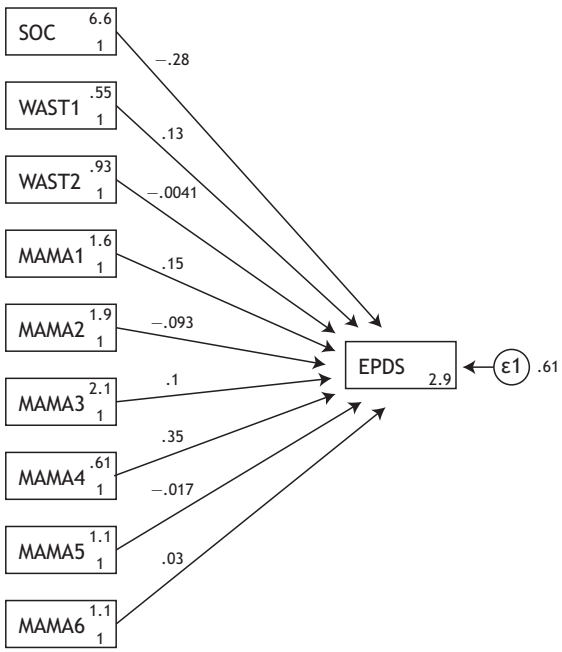

Figure 1. Correlation between EPDS, SOC and the subscales of WAST AND MAMA.
WAST 2 (Relationship tension)
WAST 1 (Emotional and Physical Abuse)
MAMA1 (Marital Relationship)
MAMA 4 (Motherhood), MAMA 6 (Breasts)
MAMA 5 (Nausea)
MAMA 3 (Body Image)
MAMA 2 (Sex)
SOC (Sense of Coherence).

model sensitivity at 76.7% and model specificity at 68.3%.[37]

Women Abuse Screening Tool.[24] The original English version of the WAST consists of 8 short questions and it is a self-report scale consisting of statements describing forms of abuse (physical, sexual and emotional). Each question has three possible answers, graded depending on the severity or duration of each form of abuse. It has good internal consistency (Cronbach α coefficient of 0.95), and it is well accepted by the women.[24–25] The first two questions of the WAST form the WAST-Short, which has been very useful for screening for abuse and most convenient questions to be asked according to the women.[24] The other questions contribute to the final assessment of the emotional abuse. In the validation study significant differences were found between the abused and non abused women on the mean overall the WAST scores (18 vs 8.8, respectively, p<.001).[24] A threshold score of 0/1 fitted the model sensitivity at 99.7% and model specificity at 64.4%.[38]

Maternal Adjustment and Maternal Attitudes (MAMA).[39] MAMA is a 60-item self-administered scale designed to measure key psychosocial dimensions related to the maternity experience.[39] A lower score indicates more positive maternal attitudes toward the pregnancy and baby and positive postnatal adjustment. The scale includes a pre- and postnatal component (here it was used the postnatal one). Internal consistency for the subscale was identified through test-retest reliability (r=0.84) and splithalf- reliability (r=0.73).[39] Construct validity has been demonstrated by finding expected relationships between the Attitudes to Pregnancy and the Baby scale and a woman's expressed feelings toward her baby, her perception of how difficult her baby is[39,40] and maternal-fetal attachment.[39–41] Alpha reliability was 0.64.

Multidimensionality of the Greek version demonstrated a six-factor structure and a threshold score of 57/58 fitted the model sensitivity at 68% and model specificity at 64.6%.[42]

Sense of Coherence (SOC).[43] The SOC scale includes of 29 items. The responses to each question are rated on a seven-point scale (scores 1 to 7) and the total score is calculated. A higher total score indicates that the individual is more likely to demonstrate coping abilities in terms of comprehensibility, manageability and meaningfulness. The scale ranges from 0 to 203 points. The Greek version of SOC[44] was used in this study.

Ethics

The study was approved by the Research Ethics Boards of Hospitals (protocol number #217/2008). All participants provided verbal informed consent prior to enrolment. Along with the questionnaires there was a cover letter explaining the purpose of the study, providing the researchers' affiliation and contact information, and clearly stating that an-

swers would be confidential and anonymity would be guaranteed in the final data reports.

Data analysis

Statistical analysis was performed using IBM SPSS Statistics version 20 and LISREL (Linear Structural Relations). Differences between participants and non-participants were assessed by Student's t-test for continuous variables and chi-square tests for categorical variables after ensuring normality, homogeneity and independent cases of the sample. The underlying levels of the comprehensive conceptual framework were checked with an explanatory factor analysis using a Varimax rotation and Principal Components Method.[45] This analysis was carried out to determine the dimensional structure of conceptual framework using the following criteria: (a) eigenvalue >1,[46] (b) variables should load >0.50 on only one factor and on other factors less than 0.40, (c) the interpretation of the factor structure should be meaningful, (d) Screeplot is accurate in the case that the means of communalities are above 0.60.[47] Computations were based on covariance matrix, as all variables were receiving values from the same measurement scale.[48] A Bartlett's test of sphericity with $p<0.05$ and a Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy of 0.6 were used in performing this factor analysis. A factor was considered as important if its eigenvalue exceeded 1.0.[49]

Additionally, a Structural Equation Modelling (SEM) was conducted by LISREL (Linear Structural Relations) to confirm that subscales principally load on to that psychosocial factor and correlate weakly with other factors, to assess tests for significance of factor loadings and orthogonality of factors,[48,50,51] a mode –based on a priori information of exploratory factor analysis– was built in order to specify latent factors, their component variables and the intercorrelations of the response variables, maximum likelihood LISREL estimates, t-values, error terms, correlation of independent variables and goodness of fit-test for the specified model were performed. Consistent with the assumption of multivariate normality, a maximum-likelihood (ML) approach to model estimation was adopted.[52–54] Multiple goodness-of-fit tests[54] were used to evaluate the models, these being the Comparative Fit Index,[55,56] and the root mean squared error of approximation (RMSEA). A CFI greater than 0.90 indicates an acceptable fit to the data [51,54,55,57,58] while a CFI equal to or greater than 0.95 indicates a good fit to the data.[51] An RMSEA with values of less than 0.08 indicate an acceptable fit to the data,[59] while values of less than 0.05 indicate a good fit to the data.[60] A statistically significant x^2 indicates that a significant proportion of variance within the data is unexplained by the model,[55] however, trivial and inconsequential variations in the data can promote a significant x^2 statistic[51] hence model evaluation is almost universally determined by model fits statistics such as CFI and RMSEA.[52,61] Goodness of fit statistics are used not to judge fit in absolute terms but instead to compare the fit of different models. Smaller values indicate a better fit. CFI and TLI, two indices such that a value close to 1 indicates a good fit. CFI stands for comparative fit index. TLI stands for Tucker–Lewis index and is also known as the non-normed fit index.[52–54]

Results

Sample characteristics

The mean age of the women was 29.76 years (Standad Error of Mean, SEM 0.537, range 20–40 years), a high (46%) proportion of women had university or even postgraduate studies. Ninety-two percent of women were in paid employment, 50% had other children and in only 2% of cases the newborn were out of wedlock (table 1). Univariate independent t tests and Chi-square test revealed that non-responders did not statistically differ from the respondents with regard to age, educational level, work status, marital status and parity. The mean scores for the validated tools were:

a. MAMA score 57.21 (SEM 2.21, SD 20.97 and range 8–150 score).

b. EPDS score 8.24 (SEM 0.50, SD 4.82 and range 0–25 score).

c. WAST score 1.38 (SEM 0.17, SD 1.67 and range 0–9 score).

d. SOC score 146.30 (SEM 2.34, SD 22.27 and range 104–198 score).

Table 1. Characteristics of the Study Sample.

	No (%)
EPDS	
No Depressive symptoms	51 (55.4)
Depressive symptoms	41 (44.6)
Mode of Delivery	
Vaginal Birth	42 (45.7)
Caesarean Section	50 (54.3)
Gravida	
Primigravida	45 (49.4)
Multigravida	46 (50.5)
Marital Status	
Married	90 (98.9)
Single	1 (1.1)
Education	
Elementary & junior high	11 (12.0)
High School	38 (41.7)
University/College Education	35 (38.4)
Postgraduate Studies	7 (7.6)
Work Status	
Housewife	32 (34.7)
Unemployed	7 (7.6)
Student	2 (2.1)
Public Sector	15 (16.3)
Private Sector	24 (26.0)
Independent	12 (13.0)
Religion	
Christian Orthodox	91 (98.9)
Catholic	0 (0.0)
Muslim	1 (1.0)
Family income per month	
500–1000 Euros	20 (23.2)
1000–2000 Euros	29 (33.7)
2000–3000 Euros	20 (23.2)
>3000	17 (19.7)

Models and correlation

Exploratory Factor analysis

The exploratory factor analysis on the items of the MAMA, WAST, SOC revealed three orthogonal factors (KMO measure of sampling adequacy=0.735 and Bartlett's test of sphericity=184.786, df=36, p<0.0005). Descriptive statistics, communalities and the correlation matrix for the validated Greek psychometric tools are presented in table 2. The correlation Matrix of EPDS and the subscales of WAST, MAMA and the SOC scale as shown in table 3 and figure 1 confirm the significant relation that was specified and implied. As the screeplot and component plot in rotated space (figure 2) indicate there are three factors in the model, explaining 60.89% of the variance (table 4). The first factor (F1) includes the WAST 2 (relationship tension), WAST 1 (emotional and physical abuse) and MAMA 1 (marital relationship) subscales, the latter includes specific questions that describe the marital relationship. The second factor (F2) is composed of subscales MAMA 4 (maternal roles and attitudes), MAMA 6 (Breasts) and MAMA 5 (Nausea), representing in a way the 'Maternity Experience'. The third factor (F3) is composed the MAMA 3 (body image), MAMA 2 (Sex) and SOC (Sense of Coherence) subscales and is considered to represent "Self Efficacy".

Table 2. Correlation Matrix of the subscales of WAST, MAMA and the SOC scale.

	SOC	WAST1	WAST2	MAMA1	MAMA2	MAMA3	MAMA4	MAMA5	MAMA6
SOC	1.000	–0.082	–0.204	–0.237	–0.145	–0.177	–0.215	–0.158	–0.049
WAST 1	–0.082	1.000	0.508	0.402	0.028	0.014	0.272	0.321	0.090
WAST 2	–0.204	0.508	1.000	0.696	0.166	0.252	0.183	0.286	0.123
MAMA 1	–0.237	0.402	0.696	1.000	0.344	0.370	0.288	0.416	0.207
MAMA 2	–0.145	0.028	0.166	0.344	1.000	0.259	0.243	0.297	0.228
MAMA 3	–0.177	0.014	0.252	0.370	0.259	1.000	0.100	0.098	0.236
MAMA 4	–0.215	0.272	0.183	0.288	0.243	0.100	1.000	0.392	0.340
MAMA 5	–0.158	0.321	0.286	0.416	0.297	0.098	0.392	1.000	0.357
MAMA 6	–0.049	0.090	0.123	0.207	0.228	0.236	0.340	0.357	1.000

SOC: Sense of Coherence, WAST: Women Abuse Screening Tool, MAMA: Maternal Adjustment and Maternal Attitudes

Table 3. Correlation Matrix of EPDS and the subscales of WAST, MAMA and the SOC scale.

Fitting target model:
Iteration 0: log likelihood= –1918.0868
Iteration 1: log likelihood= –1918.0868
Structural equation model Number of obs=90
Estimation method=mL
Log likelihood= –1918.0868

	OIM					
Standardized	**Coef.**	**Std.**	**Err.**	**z**	**p>z**	**(95% Conf. Interval)**
Structural						
EPDS ≤						
SOG	–0.2765715	0.0829228	–3.34	0.001	–0.4390973	–0.1140457
WAST 1	0.1307664	0.1005598	1.30	0.193	–0.0663272	0.3278599
WAST 2	–0.0041329	0.1236818	–0.03	0.973	–0.2465448	0.238279
MAMA 1	0.1535831	0.1292531	1.19	0.235	–0.0997483	0.4069145
MAMA 2	–0.0925046	0.0920739	–1.00	0.315	–0.2729661	0.0879569
MAMA 3	0.103431	0.0925566	1.12	0.264	–0.0779766	0.2848386
MAMA 4	0.3506101	0.0901382	3.89	0.000	0.1739424	0.5272777
MAMA 5	–0.0167306	0.1009798	–0.17	0.868	–0.2146473	0.1811861
MAMA 6	0.0304421	0.933061	0.33	0.744	–0.1524345	0.2133186
_cons	2.942241	0.6574962	4.47	0.000	1.653573	4.23091
var (e. EPDS)	0.6096703	0.0720399			0.4836323	0.7685546

LR test of model vs saturated: chi2 (0)=0.00

SEM analysis

Confirmatory factor analysis was conducted to determine whether the data were consistent with the a priori specified model that was suggested by exploratory factor analysis in order to evaluate whether the data adequately fit the model. The three factor-model was based on correlated factors that derived from the factor analysis using principal component analysis with varimax rotation. The three latent variables Marital Relationship (Subscales WAST 2, WAST 1, MAMA 1), Maternity Experience (Subscales MAMA 4, MAMA 6, MAMA 5) and Self Efficacy (MAMA 3, MAMA 2, SOC) were significantly related (Chi-square=28.45, df=24, P-value=0.24, RMSEA=0.046 p<0.05) with Maximum Likelihood method (figure 3). LISREL estimates, standard error, t-values, error terms and r^2 for all the questions that consisted each latent variables are presented in table 5. The error terms correlated significantly (with a range of: 0.32 to 421.37) Expected Cross Validation Index (ECVI)=0.79, ECVI for Saturated Model=1.01 Goodness of Fit Statistics were also estimated, Non-normed Fit Index (NNFI)= 0.96, Comparative Fit Index (CFI)=0.98, Incremental Fit Index (IFI)=0.98, Relative Fit Index (RFI)=0.92, Goodness of Fit Index (GFI)=0.93, Adjusted Good-

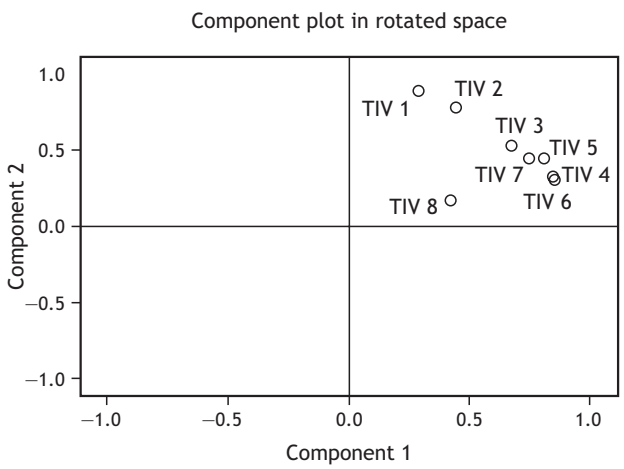

Figure 2. Component plot in rotated space.

Table 4. Exploratory factors and explained variance after rotation.

Factors		Rotation sums of squared loadings					
		Rescaled loadings	Eigen-values	(%) of variance	Cummulative variance	Cronbach's alpha	Standardised alpha
Factor I (*Marital Relationship*)	*WAST 2* (Relationship tension)	0.825	3.066	34.070	34.070	0.542	0.769
	WAST 1 (Emotional and physical abuse)	0.819					
	MAMA 1 (Marital relationship)	0.681					
Factor II (*Maternity Experience*)	*MAMA 4* (Maternal roles and attitudes)	0.735	1.280	14.226	48.296	0.628	0.630
	MAMA 6 (Breasts)	0.728					
	MAMA 5 (Nausea)	0.698					
	MAMA 3 (Body image)	0.821					
Factor III (*Self Efficacy*)	*MAMA 2* (Sex)	0.560	3.144	12.591	60.887	–0.708	–0.66
	SOC (Sense of coherence)	–0.443					

ness of Fit Index (AGFI)=0.88 (figure 3). The structure of the thematically derived 3-factor model was found to be improved, with an acceptable model fit.

Discussion

Main findings

This study has attempted for the first time to jointly use three screening tools assessing postnatal adjustment to maternal roles and attitudes (MAMA), marital/partner relationship (WAST) and sense of coherence (SOC) mediated levels of depressive symptoms during early postpartum period (indexed by EPDS). The integrated model including direct effects of marital relationship, maternal experience and self-efficacy proved to be the best model. Epidemiological research of psychosocial factors that contribute to postnatal depressive symptomatology is important in order to provide information about which populations are most at risk and can also be helpful in informing decisions and healthcare services.[3,12]

Previous literature has suggested factors that might mediate the development of postnatal depressive symptomatology.[1,3,12] This exploratory study has described, explored and tested a self-constructed conceptual framework to help understand the relative impact of postnatal adjustment to maternal roles and attitudes (MAMA), marital/partner relationship (WAST) and sense of coherence (SOC) on levels of depressive symptoms during early postpartum period. Our results suggest that screening for postnatal mental vulnerability favours the use of combination of validated psy-

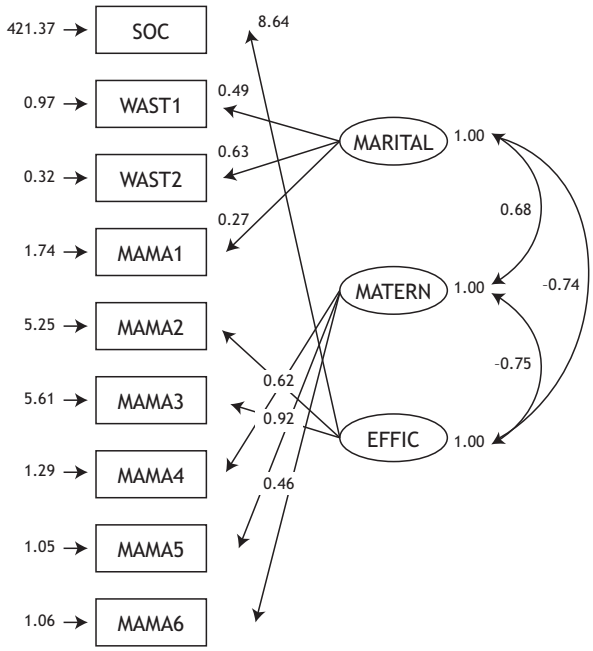

Figure 3. Confirmatory Factor Analysis for the model.
Factor I (Marital Relationship)
WAST 2 (Relationship tension)
WAST 1 (Emotional and Physical Abuse)
MAMA1 (Marital Relationship)
Factor II (Maternity)
MAMA 4 (Motherhood)
MAMA 6 (Breasts)
MAMA 5 (Nausea)
Factor III (Self Efficacy)
MAMA 3 (Body Image)
MAMA 2 (Sex)
SOC (Sense of Coherence)

chometric tools such as MAMA, WAST and SOC. Marital relationship, maternal experiences and self-efficacy have been significantly associated with levels of depressive symptoms during early postpartum period.[3,7,12,62] Previous studies[6,12,15,63,64] have shown a strong correlation between the depressive symptomatology and other screening instruments used.

Moreover, results of this study replicate and further highlight previously published data that underlines that the presence of the specific psychosocial risk factors increases the risk of perinatal mental vulnerability.[7,12,62] In particular, the structural equation modelling (SEM) supported the relationship between positively and negatively valued screening instruments (SOC, WAST, MAMA) and the following latent variables: the marital relationship, maternity experience and self-efficacy.[7,12,15,17,62–63]

Firstly, Marital Relationship (Factor I≥as described by WAST subscales and MAMA1 subscale) and especially lack of or disappointment with partner support, poor marital relationship and emotional/physical abuse has been associated with high levels of postpartum anxiety and depression.[3,13,22–26] Secondly, Maternity Experience (Factor II≥as described by MAMA subscales) and especially postnatal roles and attitudes towards their infant can be as useful as mood changes for evaluation of mothers.[15,18,19] Thirdly, Self-Efficacy (Factor III≥as described by SOC and MAMA subscales) and especially attitudes regarding body image, sex and coping resources and options of dealing with the stressor, has been demonstrated that serve as a mediator or buffer for psychological distress.[3] Therefore, early postnatal mental health screening and a comprehensive psychosocial assessment would be beneficial for the clinical practice in primary care settings.[12,28] The combined use of these three tools is recommended in daily practice in cases that the health professional would like to explore borderline depressive symptomatology during postnatal period. The additional benefit would be to provide a woman centred care to the new mother.

Limitations

There are a number of limitations that should be taken into account for the interpretation of our results. The design of the study was of cross sectional nature entailing only one point assessment in the early postpartum period, whereas psychosocial factors may also affect depression symptoms during pregnancy and persist in later life periods critical for the mother and the newborn, such as during lactation. Moreover, the depressive symptomatology, the maternal experience, the emotional abuse and sense of coherence were assessed with only paper-and pencil measures (i.e. the EPDS, MAMA, WAST and the SOC) without further assessment. Additionally, the administration of psychometric questionnaires during the early

Table 5. LISREL estimates (maximum likelihood) for the conceptual framework.

Independent variables		Measurement equations				
		Estimates	Standard error	t values	Error terms	R^2
	WAST 2 (Relationship tension)	0.63	0.086	7.31	0.32	0.55
Factor I (*Marital Relationship*)	*WAST 1* (Emotional and physical abuse)	0.49	0.12	4.10	0.97	0.19
	MAMA 1 (Marital relationship)	3.27	0.35	9.44	1.74	0.86
	MAMA 4 (Maternal roles and attitudes)	0.62	0.16	3.82	1.29	0.23
Factor II (*Maternity Experience*)	*MAMA 6* (Breasts)	0.46	0.14	3.25	1.06	0.17
	MAMA 5 Nausea)	0.92	0.18	5.06	1.05	0.45
	MAMA 3 (Body image)	−1.13	0.34	-3.30	5.61	0.18
Factor III (*Self Efficacy*)	*MAMA 2* (Sex)	−1.34	0.35	-3.79	5.25	0.26
	SOC (Sense of coherence)	8.64	2.88	3.00	421.37	0.15

postpartum period (on average three days after giving birth) may have caused inconvenience to the new mothers[65] and may not have reflected the ability to distinguish women who did and did not have psychosocial problems a short time following delivery. However, EPDS has been validated for use soon after the birth.[7]

In this study, we relied on retrospective maternal reports for the timing of postpartum difficulties, and recall bias may also have adversely affected our findings. In spite of the above concerns, the size of our sample was satisfactory for explanatory and SEM analysis.[65–67] On the positive side as well, the study was conducted in a rather culturally homogeneous prefecture of Greece that captured all maternity units from which intensive efforts were made to recruit a representative sample, validated instruments were used to assess exposures and outcomes, whereas the study was coordinated by a single midwife, who succeeded in collaboration with her colleagues to minimize refusal rates and losses.

Conclusion

The results of this study signify the need to remove the stigma around perinatal mental disorders, postpartum adjustment difficulties and abuse as identified in the postpartum period. The main effort when intervening in order to prevent perinatal mental disorders should come from screening, so as women who are positive on screening are to have appropriate and timely care. Results of this study have implications for the prevention and intervention of postnatal mental vulnerability both of which need to be intensified in order to minimise perinatal mental morbidity and mortality.

List of abbreviations used

WAST: Women Abuse Screening Tool

SOC: Sense of Coherence

EPDS: Edinburgh Postnatal Depression Scale

MAMA: Maternal Adjustment and Maternal Attitudes

Πρώιμη ανίχνευση της επιλόχειας ψυχικής ευπάθειας

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Ένας αυξανόμενος αριθμός ερευνών έχει αναδείξει τον αντίκτυπο των προβλημάτων ψυχικής υγείας των μητέρων κατά τη διάρκεια της λοχείας και τον σημαντικό ρόλο των επαγγελματιών υγείας που εργάζονται στην Πρωτοβάθμια Φροντίδα Υγείας για την έγκαιρη ανίχνευση των γυναικών που μπορεί να διατρέχουν κίνδυνο. Η παρούσα μελέτη είχε ως πρωταρχικό στόχο να περιγράψει, να ερευνήσει και να δοκιμάσει ένα *a priori* υποθετικό εννοιολογικό μοντέλο για την εμπειρία κατά τη διάρκεια της λοχείας, τον προσδιορισμό των σχέσεων μεταξύ επιλόχειας ψυχικής ευπάθειας και την επιλόχεια προσαρμογή σε μητρικούς ρόλους και στάσεις, τη συζυγία και την αίσθηση συνοχής. Τρεις σταθμισμένες αυτοσυμπληρούμενες ψυχομετρικές κλίμακες (WAST, MAMA, SOC) χρησιμοποιήθηκαν για την αξιολόγηση των μεταβλητών του εννοιολογικού πλαισίου. Τα εννοιολογικό μοντέλο ελέγχθηκε με τη χρήση του λογισμικού IBM SPSS. Χρησιμοποιήθηκαν οι κάτωθι στατιστικές δοκιμασίες: Student's t-test, chi-square tests, Explanatory factor analysis using a Varimax rotation Principal Components Method, Confirmatory analysis. Η παραγοντική διερευνητική ανάλυση επιβεβαίωσε τον ρόλο της κλίμακας SOC, συγκεκριμένων υποκλιμάκων της MAMA (οι μητρικοί ρόλοι και στάσεις, το σεξ, η εικόνα του σώματος, συμπτώματα όπως ναυτία) και των υποκλιμάκων της WAST (ένταση στη συζυγία και συναισθηματική και σωματική κακοποίηση), (KMO μέτρο για την επάρκεια της δειγματοληψίας=0,735 και η δοκιμή του Bartlett για σφαιρικότητα=184.786, d=36, p=0,0005). Οι λανθάνουσες μεταβλητές που επιβεβαιώθηκαν με την ανάλυση SEM ήταν: η φύση της συζυγίας, το βίωμα της μητρότητας και η αίσθηση αυτο-επάρκειας (Chi-square=28,45, df=24, P-value=0,24, RMSEA=0,046 p<0,05). Η φύση της συζυγίας (παράγοντας I: Eigenvalue=3,066) και ιδιαίτερα η αίσθηση έλλειψης υποστήριξης ή η απογοήτευση από τον σύζυγο, η μη ποιοτική συζυγία και η συναισθηματική/φυσική κακοποίηση από τον σύντροφο φαίνεται να έχουν σημαντική συσχέτιση με το άγχος και την κατάθλιψη κατά τη διάρκεια της λοχείας. Το βίωμα της Μητρότητας (παράγοντας II: Eigenvalue=1,280), δηλαδή οι ρόλοι και οι στάσεις απέναντι στο νεογνό, θα μπορούσε να είναι χρήσιμη παράμετρος για την εκτίμηση των αλλαγών της διάθεσης την περίοδο της λοχείας, για την αξιολόγηση των μητέρων. Η αίσθηση αυτο-επάρκειας (παράγοντας III: Eigenvalue=3,144) περιλαμβάνει τις στάσεις των λεχωίδων όσον αφορά στην εικόνα του σώματος, στο σεξ και στις μεθόδους αντιμετώπισης του άγχους, και φαίνεται να έχει σημαντική συσχέτιση με ψυχικές διαταραχές κατά τη λοχεία. Τα αποτελέσματα αυτής της μελέτης συμβάλλουν στην πρόληψη και στην παρέμβαση όταν υπάρχουν δυσκολίες προσαρμογής κατά τη διάρκεια της άμεσης λοχείας, με στόχο να ενισχυθεί το πλαίσιο των δραστηριοτήτων των επαγγελματιών υγείας στην Πρωτοβάθμια Φροντίδα Υγείας, προκειμένου να ελαχιστοποιηθεί η περιγεννητική ψυχική ευπάθεια.

Λέξεις ευρετηρίου: Καταθλιπτικά συμπτώματα, λοχεία, κακοποίηση, μητρική εμπειρία, αυτο-επάρκεια.

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Research article
Ερευνητική εργασία

Clinical and cognitive factors affecting psychosocial functioning in remitted patients with bipolar disorder*

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Impaired interpersonal, social, and occupational functioning is very often observed in patients with bipolar disorder, not only at the acute stages of the illness but in remission as well. This finding raises the question of multiple factors that might affect psychosocial functioning in bipolar patients, such as residual subsyndromal symptoms and neuropsychological deficits. Social cognition impairment, especially impaired Theory of Mind (ToM), might also play an important role in bipolar patients' every-day functioning, similarly to what was found in patients with schizophrenia. The present study aimed to investigate the potential effect of clinical and cognitive factors on the psychosocial functioning of patients with bipolar disorder during remission, assessing ToM along with a broad range of basic cognitive functions. Forty-nine patients with bipolar disorder type I in remission and 53 healthy participants were assessed in general intelligence, working memory, attention, speed processing, verbal learning and memory, and executive functions using a comprehensive battery of neuropsychological tests. The Faux Pas Recognition Test was used to assess ToM. The two groups were matched for gender, age and education level. The Hamilton Rating Scale for Depression (HDRS), the Young Mania Rating Scale (YMRS), and the Brief Psychiatric Rating Scale (BPRS) were also administered to the patients. Every-day functioning was assessed with the Global Assessment of Functioning (GAF). In order to examine the contribution of many factors in psychosocial functioning, we used hierarchical multiple regression analysis. Bipolar patients presented significant impairment compared to healthy participants in all the basic cognitive functions tested with the exception of verbal memory. Moreover, patients had significant poorer performance than healthy controls in overall

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and cognitive ToM but not in affective ToM as measured by Faux Pas. Psychosocial functioning in patient group was significantly correlated to symptom severity–especially depressive ($p<0.001$) and psychotic symptoms ($p=0.001$), history of psychotic episodes ($p=0.031$) and ToM, overall ($p=0.001$) as well as its cognitive ($p=0.023$) and affective ($p=0.004$) components. Only the contribution of ToM in psychosocial functioning remained significant in the final multiple regression model. The findings of the current study indicate that residual symptoms and cognitive dysfunctions, especially deficits in social cognition, negatively affect psychosocial functioning of remitted patients with bipolar disorder. Moreover, our results suggest that ToM may play a central role in these patients' functioning. ToM is a mediator of the relationship between other clinical or cognitive variables and functioning, while it has also significant effect on social skills independently of other factors. Therefore, specific therapeutic interventions targeting social cognitive dysfunction might improve functional outcome in bipolar disorder. Putative contribution of other clinical characteristics (comorbid personality disorders, substance abuse, anxiety) and psychosocial factors (stigma, self-stigma, lack of social network) in bipolar patients' functioning should be examined in future studies.

Key words: Social functioning, cognitive dysfunction, Theory of Mind, social cognition, bipolar disorder, remission.

Introduction

Despite its episodic course, bipolar disorder (BD) causes persistent impairment of psychosocial and occupational functioning. Many studies have shown that patients with bipolar disorder exhibit significant deficits in functioning even during remission.[1,2] A literature review of previous studies on therapeutic outcomes revealed that after recovery of the first manic or mixed episode of the disease, 57–65% of patients remained unemployed and 80% had at least partial vocational disability.[3] Despite the chronicity and high frequency of social dysfunction in patients with BD the causes of dysfunction remain largely unknown so far.

Previous studies suggest that during the long course of the disease, persistent, residual or subsyndromal symptoms have a negative impact on patients' functioning even if they remain in remission.[4–7] However, the frequency of social dysfunction in fully remitted patients, i.e. in sustaining long-term euthymia, indicates that other factors, in addition to clinical symptoms, have also significant impact on functioning. Previous studies and a recent meta-analysis have revealed a negative effect of cognitive dysfunction on psychosocial functioning of BD patients.[8] Moreover, this effect has been also found in euthymic or chronic patients.[9] As it has already been shown by many studies, deficits in a wide range of cognitive domains are a key feature of BD and they also persist in remission.[10–12]

Many studies in schizophrenia have also shown the impact of cognitive dysfunction on psychosocial functioning to the same or even greater degree than what was found in BD.[13,9] Research findings also support that social cognition, i.e. cognitive functions associated with interpersonal interaction, mediates between basic cognitive skills and global functioning in schizophrenia. More precisely, it has been found that deficits in Theory of Mind (ToM), the ability to perceive mental states of other people (such as beliefs, intentions and emotions), have a significant contribution in impaired social functioning of these patients probably to a greater extent than any other concurrent cognitive deficit.[14] ToM deficits were also found in BD that may persist even in remission.[15,16] However, few studies examined the potential impact of ToM on psychosocial functioning in BD[17–21] and there is only one study so far that examined the effect of ToM along with other cognitive factors (attention and executive functions).[22]

The purpose of the present study was to examine the effect of clinical and cognitive factors –including ToM– on psychosocial functioning in remitted patients with BD. To our knowledge, this is the first study examining the specific effect of ToM on psy-

chosocial functioning taking also into account the effect of a broad range of basic cognitive functions.

Material and Methods

Participants and procedures

Forty-nine patients (31 female and 18 male) aged 22–65 years meeting the DSM-IV-TR criteria for BD type-I[23] were recruited along with 53 healthy participants (31 female and 22 male). All the patients participated in the study were in symptomatic remission (see below for remission criteria). Patient and control groups were matched for gender, age and education level. The clinical sample was recruited from the outpatient services of the General Hospital "G. Gennimatas" and the Eginition Hospital in Athens. Healthy participants were recruited from the local communities.

All patients were receiving medication at the time of assessment. In particular, all of them were receiving mood stabilizers (lithium, divalproex sodium etc.) and some of them were additionally on antipsychotics (59.2%), antidepressants (36.7%) and benzodiazepines (28.6%). Antipsychotic medication dosage was converted into chlorpromazine equivalents.[24,25]

The exclusion criteria for all participants were: age beyond 65 years old, mental retardation, history of head injury or any neurological disorder, history of perinatal events, history of CNS infections, alcohol or substance abuse in the preceding 6 months and receiving electroconvulsive therapy within last year. Inclusion criteria for the control subjects were no personal history of psychiatric disorder or family history (first degree relatives) of psychosis or bipolar disorder. All participants were Greek native speakers. All participants had been informed about the research procedures and given written informed consent as approved by the local Ethics Committee. Additional information for patients was obtained from their medical records and treating physicians.

Clinical assessment

Patients' psychosocial functioning was assessed by Global Assessment of Functioning (GAF).[26] Symptom severity in patients with BD was evaluated by valid and widely used clinical scales: (a) the Brief Psychiatric Rating Scale (BPRS),[27] which assesses psychotic symptoms, (b) the Hamilton Depression Rating Scale (HDRS),[28] which assesses depressive symptomatology, and (c) the Young Mania Rating Scale (YMRS),[29] which assesses manic symptomatology. All the patients were euthymic (i.e. a score ≤7 on the HDRS and <8 on the YMRS), in symptomatic or syndromic remission according to the criteria recommended by the International Society for Bipolar Disorders (ISBD).[30]

Neuropsychological assessment

A neuropsychological battery assessing a wide range of cognitive functions was administered to all participants. The Vocabulary subscale (WAIS-Vocabulary) from Wechsler Adult Intelligence Scale (WAIS)[31] was used to estimate general intellectual ability, because it is considered as the scale with the highest correlation with individual's general intelligence. The Block Design (WAIS-Block design) and Digit Span (WAIS-Digit span) subscales were used to assess visuospatial and verbal working memory, respectively. Executive functions were examined using three different tasks: the Stroop Color-Word test (Stroop),[32] the Wisconsin Card Sorting Test-64 version (WCST),[33] and the Trail Making Test, part A & B (Trails).[34] The Stroop-Interference, WCST-Categories, WCST-Perseverative errors and Trails-B were used as indicators of executive functioning. Moreover, the Stroop-Word and Trails-A scores were used in this study as measures of sustained attention and processing speed. Verbal memory was assessed by the Babcock Story Recall Test (Babcock)[35] – immediate and delayed recall scores.

ToM was evaluated by the Faux Pas Recognition Test (Faux Pas).[36] A Faux Pas occurs when someone says something without thinking that the person who hears it, may not want to hear it or be offended or hurt by it. The test consists of 20 stories arranged in random order–half of which contained a social faux pas and half of which did not (control stories). In the present study, the sum of correct faux pas detections and correct rejections in control stories (non-Faux Pas stories) were measured (Faux Pas-detection score) as an index of overall ToM ability. Two specific dimensions of ToM were also assessed through the scores in related, particular questions of the task. Understanding intentions and beliefs of the character that made the faux pas (Faux Pas-cognitive un-

derstanding) was used as a cognitive component of ToM (understanding intentions, thoughts, beliefs of others), while understanding the emotional impact of faux pas on the "victim" of each story (Faux Pas-affective understanding) was used as an affective component of ToM (understanding the emotional state of others).

Statistical analysis of the data

The normality of distribution was examined by the means of Kolmogorov-Smirnov tests and parametric or non-parametric tests were used as appropriate. For the comparisons between BD patients and healthy controls in demographic characteristics t-test and Mann-Whitney U test were used for quantitative variables and x^2 test for categorical variables. Patients scores on different neuropsychological tests (except ToM) were converted to z-scores using control's means and standard deviations and then averaged within domains to yield a domain composite score. The bivariate associations between variables were examined with Spearman rho correlation coefficients. Hierarchical multiple regression analysis was also used to explore the independent contribution of several variables on psychosocial functioning. Level of significance for all tests was set at p=0.05. Statistical analyses were performed using SPSS version 15.0.

Results

Demographic and clinical characteristics of the sample are presented in table 1. As expected, there were no significant differences between patients and controls with respect to gender, age or years of education (x^2=0.24, p=0.622). Table 1 also displays the patients' values regarding the severity of symptoms, psychosocial functioning and other clinical variables. Moreover, 34 patients (69.4%) were in symptomatic remission (euthymia for at least 8 weeks) and the rest of them in syndromic remission (only subclinical symptoms during the last 8 weeks). Twenty-eight patients (57.1%) had a history of episodes with psychotic symptoms.

The comparisons between BD patients and healthy participants regarding to their performance in neuropsychological tests are presented in table 2. BD patients showed significant deficits in general intellectual ability, attention, speed processing, working memory, visuospatial abilities and executive functions compared to healthy controls. However, there was no significant difference in verbal memory score between patients and healthy controls. Regarding ToM assessment, patients had significantly poorer performance than healthy controls in overall ToM (Faux Pas detection score) and in cognitive ToM but showed no deficit in affective ToM.

Table 1. Demographic and clinical characteristics of patients with bipolar disorder (BD) and healthy participants.

	Healthy controls (n=53) Mean (SD)		BD-Patients (n=49) Mean (SD)		Statistics	p
Age (years)	43.0	(11.6)	43.4	(12.1)	–0.17	0.868
Education (years)	13.3	(3.5)	13.1	(3.3)	0.26	0.798
Age of onset (years)	–	–	27.8	(7.7)		
Duration of illness (years)	–	–	14.9	(9.6)		
Number of hospitalizations	–	–	3.4	(3.1)		
Antipsychotic daily dosage (mg)[a]	–	–	209.4	(229.1)		
BPRS	–	–	27.2	(6.0)		
HDRS	–	–	4.6	(4.4)		
YMRS	–	–	3.6	(3.2)		
GAF	–	–	68.9	(10.6)		

[a]Chlorpromazine equivalents, *HDRS*=Hamilton Depression Rating Scale, *YMRS*=Young Mania Rating Scale, *BPRS*=Brief Psychiatric Rating Scale, *GAF*=Global Assessment of Functioning

Table 2. Cognitive performance of patients with bipolar disorder (BD) in comparison to healthy controls.

Cognitive Functions	Healthy controls (n=53) Raw Score Mean (SD)		BD Patients (n=49) Raw Score Mean (SD)		Z Score Mean (SD)		t/z[a]	p
General intelligence	11.9	(1.6)	10.9	(2.9)	–0.61	(1.80)	–2.01	0.048
Attention & Speed processing					–0.54	(1.18)	–3.22	0.001
Stroop-word	97.3	(15.9)	85.5	(24.8)				
Trails A	42.0	(26.1)	50.8	(31.7)				
Working memory	4.7	(1.4)	4.0	(1.2)	–0.50	(0.85)	–2.55	0.011
Visuospatial ability	10.9	(1.8)	8.7	(2.1)	–1.21	(1.15)	–4.61	<0.001
Verbal memory					–0.08	(1.07)	–0.38	0.708
Babcock-Immediate recall	14.3	(3.7)	14.8	(4.5)				
Babcock-Delay recall	14.4	(3.7)	13.2	(4.0)				
Executive functions					–0.69	(0.88)	–4.40	<0.001
Stroop-Interference	–0.2	(9.8)	–2.4	(9.4)				
WCST-Categories	3.1	(1.2)	2.2	(1.6)				
WCST-Perseverative errors	9.8	(7.8)	14.5	(9.2)				
Trails B	98.2	(70.9)	145.2	(84.9)				
Theory of mind								
Faux Pas-Detection	25.9	(4.3)	24.0	(4.8)			–2.06	0.042
Faux Pas-Cognitive understanding	6.3	(2.2)	4.8	(2.2)			–3.39	0.001
Faux Pas-Affective understanding	7.0	(2.3)	6.3	(2.6)			–1.48	0.142

[a]T test (t scores) for Verbal Memory, Executive Functions and Theory of Mind, Mann-Whitney test (z scores) for the rest variables. *WAIS*=Wechsler Adult Intelligence Scale, *WCST*=Wisconsin Card Sorting Test

Table 3 displays correlations of psychosocial functioning (as measured with GAF) with demographic, clinical, and cognitive variables within the patient group. Significant correlations were found with severity of symptoms, particular depressive (HDRS) and psychotic (BPRS) symptoms, and with ToM, both overall ToM ability as well as cognitive and affective component. In addition, no significant difference was found between genders in functioning (males 65.8±13.6, females 69.3±0.3, t=1.44, p=0.155). On the contrary, patients with a history of psychotic episode (66.1±11.3) were significantly impaired in functioning compared to those without psychotic history (72.5± 8.4, t=–2.22, p=0.031).

The independent effect of certain clinical or cognitive factors on psychosocial functioning and the possible mediating effect of ToM on these relationships were explored by means of multiple regression analysis. As ToM is the factor that probably is associated with both symptoms and basic cognitive functions, hierarchical method was used in the regression analysis, in which other variables were entered in the first step, and ToM in the second step, as predictors of the GAF score, which was the dependent variable (table 4). In the first analysis, HDRS and BPRS scores were entered in the first step. In this step only the BPRS score was significant. In the final model, which explains 30% of the psychosocial functioning variance, only the variance accounted for by ToM was significant. In the second analysis, the effect of a history of psychotic episodes was initially entered, which was statistically significant at first but became non-significant after ToM was entered in the equation. In the third analysis, the effect of basic cognitive functions through a total performance score (average z scores of all cognitive functions except ToM) was entered in

Table 3. Correlations of psychosocial functioning in patients with bipolar disorder.

	GAF	
	rho	p
Age (years)	0.01	0.941
Education (years)	0.02	0.892
Age of onset (years)	0.10	0.512
Duration of illness (years)	-0.04	0.771
Number of hospitalizations	–0.10	0.521
Antipsychotic daily dosage (mg/d)[a]	–0.22	0.120
BPRS	–0.47	0.001
HDRS	–0.72	<0.001
YMRS	–0.34	0.100
General intelligence	0.12	0.428
Attention & Speed processing	0.13	0.369
Working memory	0.15	0.308
Visuospatial ability	0.07	0.638
Verbal memory	0.13	0.377
Executive functions	0.02	0.899
Theory of mind		
Overall	0.45	0.001
Cognitive	0.33	0.023
Affective	0.41	0.004

[a]Chlorpromazine equivalents, *HDRS*=Hamilton Depression Rating Scale, *YMRS*=Young Mania Rating Scale, *BPRS*=Brief Psychiatric Rating Scale, *GAF*=Global Assessment of Functioning

the first step. This effect was not found significant, while in the second step, which explained 22% of the psychosocial functioning variance, the effect of ToM was significant.

Discussion

The findings of the present study indicate that both subclinical symptoms and cognitive dysfunction, particularly dysfunction in social cognition, have a negative effect on remitted BD patients' psychosocial functioning. In addition, current findings highlight the central role of ToM in these patients' functioning. ToM is the factor that mediates the relationship between other clinical and cognitive variables and functioning. In addition, ToM has a significant impact on social skills independently of other factors.

Previous studies also found a significant correlation between ToM and functioning in BD,[20–22] although there have also been contrary findings.[17–19] Different measures of both functioning and ToM in these studies may be largely responsible for the contradictory results. However, only one study[22] evaluated the effect of ToM along with the effect of other cognitive functions (sustained attention and executive functions) and symptoms on functioning. This study found that the relationship between ToM deficits and poor functioning was not affected by these particular cognitive functions, whereas was influenced by the severity of subclinical depressive symptoms. In our study, in which for the first time many cognitive functions were included simultaneously in the analysis, the relationship between ToM and functioning was independent of any other clinical or cognitive factor.

Deficits in basic cognitive functions found in the present study –in all functions evaluated, except for verbal memory– are in agreement with the findings of previous studies in euthymic patients.[10] Moreover, this study found ToM deficits consistent with many previous studies in patients during remission.[15,16] In particular, identified deficits were related to cognitive rather than emotional component of ToM, as revealed in all previous studies that distinguished those two components during ToM assessment.[37–39]

The mediating role of ToM in the relationship between symptoms or cognitive deficits and social skills in BD patients, seems similar to what has been found regarding these relationships in schizophrenia.[14] The present study revealed significant correlations between functioning and depressive and psychotic symptoms, although patients had only subclinical symptoms. The impact of these symptoms on functioning in BD during remission has also emerged from previous studies.[4–7] Contrary to the majority of previous studies,[8] no correlation was found between functioning and any cognitive function other than ToM in this study. However, it should be noted that other studies have not found a direct correlation between cognition and functioning,[40,41] while even across positive studies the findings vary widely regarding which particular cognitive functions were found to be related to social dysfunction.[9] On the other hand, social cognition

Table 4. The effect of clinical and cognitive variables on psychosocial functioning: Hierarchical multivariate regression.

	Model summary of each step			Contribution of each variable		
Variables	**R^2 change**	**F change**	**p**	**B**	**t-value**	**Predictor p**
Analysis1						
Step1	0.15	4.14	0.022			
Depressive symptoms*				–0.11	–0.67	0.504
Psychotic symptoms**				–0.33	–2.11	0.040
Step 2	0.15	9.30	0.004			
Depressive symptoms				–0.14	–0.98	0.331
Psychotic symptoms				–0.23	–1.58	0.121
Theory of Mind ***				0.39	3.05	0.004
Final model	0.30	6.37	0.001			
Analysis 2						
Step1	0.09	4.29	0.044			
History of psychotic episodes				–0.29	–2.07	0.044
Step 2	0.17	10.29	0.002			
History of psychotic episodes				–0.24	–1.87	0.069
Theory of Mind				0.42	3.21	0.002
Final model	0.26	7.72	0.001			
Analysis 3						
Step 1	0.00	0.01	0.932			
Basic cognitive functions[a]				0.01	0.08	0.932
Step 2	0.22	12.57	0.001			
Basic cognitive functions				0.21	1.47	0.147
Theory of Mind				0.51	3.55	0.001
Final model	0.22	6.29	0.004			

Dependent variable: Global Assessment of Functioning (GAF) total score, *Depressive symptoms: Hamilton Depression Rating Scale (HDRS) total score, **Psychotic symptoms: Brief Psychiatric Rating Scale (BPRS) total score, ***Theory of Mind (ToM): Faux Pas-detection score, [a]Basic cognitive functions: mean average of z scores of all cognitive functions except Theory of Mind

and especially ToM may be a mediator of the effect of cognitive impairment and symptoms on social functioning, as it has been found that the degree of ToM dysfunction is strongly related to both symptom severity[42] and neurocognition in BD.[39] It is likely that ToM similarly mediates the effect of previous psychotic BD episodes on patients' functioning, as shown by the present study. BD patients with a history of psychotic episodes appear to have a modest but significant impairment in cognitive functioning, according to a recent review of relevant research.[43] In addition, a recent study showed that these patients are also impaired in ToM, particularly in the emotional component of ToM, compared to the BD patients without psychotic history.[39]

According to our findings, approximately 30% of the variance in psychosocial functioning is explained by both symptoms and social cognition impairment, indicating that these factors have important contribution in BD remitted patients' social dysfunction. However, the contribution of other clinical (coexisting personality disorders, substance abuse and generalized anxiety) and psychosocial factors (stigma, self-stigma, lack of social network) in BD patients' functioning should be examined.

A methodological limitation of the present study that should be noted is that functioning was measured by a single overall score, which did not allow the assessment of specific domains (e.g. independent living, work, interpersonal relations). Furthermore,

other dimensions of social cognition that were not assessed may also be particularly important in BD, such as recognizing emotions or empathy. Finally, it was not possible to eliminate the impact of medication, as in all previous studies, yet only the daily doses of antipsychotic drugs were accounted for in the analysis.

In conclusion, the findings of this study suggest that social cognition deficits particularly in ToM, is a key determinant of psychosocial functioning in BD patients regardless of the severity of psychopathology. Moreover, ToM is a mediator of the impact of subclinical symptoms and basic cognitive deficits on social dysfunction, as observed in euthymic states of BD. Therefore, specialized therapeutic interventions for enhancing social cognition are expected to have beneficial effect on general functioning of BD patients.

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Κλινικοί και νοητικοί παράγοντες που επιδρούν στην ψυχοκοινωνική λειτουργικότητα των ασθενών με διπολική διαταραχή σε ύφεση

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Πολύ συχνά παρατηρείται στη διπολική διαταραχή μειωμένη διαπροσωπική, κοινωνική και επαγγελματική λειτουργικότητα, όχι μόνο στις οξείες φάσεις της νόσου αλλά και κατά τις περιόδους ύφεσης. Το εύρημα αυτό εγείρει ερωτήματα για την παράλληλη επίδραση πολλών παραγόντων, όπως τα εμμένοντα υποκλινικά συμπτώματα αλλά και τα νευροψυχολογικά ελλείμματα, στην ψυχοκοινωνική δυσλειτουργία των διπολικών ασθενών. Η δυσλειτουργία της κοινωνικής νόησης και ιδιαίτερα της Θεωρίας του Νου (ΘτΝ) είναι επίσης πιθανό να παίζει σημαντικό ρόλο στη λειτουργικότητα των ασθενών αυτών, κατ' αντιστοιχία με ό,τι έχει βρεθεί σε ασθενείς με σχιζοφρένεια. Η παρούσα μελέτη είχε ως σκοπό να διερευνήσει την πιθανή επίδραση κλινικών και νοητικών παραγόντων στην ψυχοκοινωνική λειτουργικότητα ασθενών με διπολική διαταραχή κατά την ύφεση της νόσου, συνεκτιμώντας τη ΘτΝ και ένα ευρύ φάσμα βασικών νοητικών λειτουργιών. Σαράντα εννέα ασθενείς με διπολική διαταραχή τύπου Ι σε ύφεση και 53 υγιείς συμμετέχοντες αξιολογήθηκαν με μια συστοιχία νευροψυχολογικών δοκιμασιών για το γενικό νοητικό δυναμικό, τις οπτικοχωρικές ικανότητες, τη μνήμη εργασίας, την προσοχή, την ταχύτητα επεξεργασίας, τη λεκτική μνήμη και τις εκτελεστικές λειτουργίες. Η ΘτΝ αξιολογήθηκε με τη δοκιμασία αναγνώρισης ατοπήματος (Faux Pas Recognition Test). Οι δύο ομάδες εναρμονίστηκαν ως προς το φύλο, την ηλικία και το επίπεδο εκπαίδευσης. Στους ασθενείς χορηγήθηκαν επίσης οι κλινικές κλίμακες: Hamilton Rating Scale for Depression (HRSD), Young Mania Rating Scale (YMRS), Brief Psychiatric Rating Scale (BPRS), ενώ για την εκτίμηση της

ψυχοκοινωνικής λειτουργικότητας χρησιμοποιήθηκε η κλίμακα Global Assessment of Functioning (GAF). Προκειμένου να ελεγχθεί ταυτόχρονα η συμβολή περισσότερων μεταβλητών στην ψυχοκοινωνική λειτουργικότητα, διενεργήθηκε ανάλυση πολλαπλής παλινδρόμησης με ιεραρχική μέθοδο. Οι ασθενείς με διπολική διαταραχή παρουσίασαν σε σύγκριση με τους υγιείς μάρτυρες σημαντικά ελλείμματα σε όλες τις βασικές νοητικές λειτουργίες πλην της λεκτικής μνήμης. Είχαν επίσης σημαντικά φτωχότερη επίδοση από τους υγιείς στη συνολική βαθμολογία του Faux Pas και στη γνωστική συνιστώσα της ΘτΝ, αλλά όχι στη συναισθηματική συνιστώσα της ΘτΝ. Βρέθηκαν σημαντικές συσχετίσεις της ψυχοκοινωνικής λειτουργικότητας των ασθενών με τη βαρύτητα της συμπτωματολογίας, ειδικότερα της καταθλιπτικής (p<0,001) και της ψυχωσικού τύπου (p=0,001), με την ύπαρξη ιστορικού ψυχωσικών επεισοδίων (p=0,031) και με τη ΘτΝ, τόσο με τη γενική ικανότητα (p=0,001) όσο και με τη γνωστική (p=0,023) και τη συναισθηματική συνιστώσα (p=0,004). Κατά την ανάλυση πολλαπλής παλινδρόμησης, μόνον η επίδραση της ΘτΝ στην ψυχοκοινωνική λειτουργικότητα παρέμεινε σημαντική. Τα ευρήματα της παρούσας μελέτης αναδεικνύουν ότι τόσο τα υποκλινικά συμπτώματα όσο και οι νοητικές δυσλειτουργίες, ειδικότερα οι δυσλειτουργίες στην κοινωνική νόηση, επιδρούν αρνητικά στην ψυχοκοινωνική λειτουργικότητα των ασθενών με διπολική διαταραχή κατά την ύφεση της νόσου. Επιπλέον, καταδεικνύουν τον κεντρικό ρόλο που παίζει η ΘτΝ στη λειτουργικότητα των ασθενών αυτών. Η ΘτΝ είναι ο παράγοντας που διαμεσολαβεί στη σχέση άλλων κλινικών και νοητικών παραμέτρων με τη λειτουργικότητα και έχει επιπλέον σημαντική επίδραση στις κοινωνικές δεξιότητες ανεξάρτητα από άλλους παράγοντες. Κατά συνέπεια, ειδικές θεραπευτικές παρεμβάσεις που βελτιώνουν την κοινωνική νόηση, αναμένεται να έχουν ιδιαίτερα ευεργετικά αποτελέσματα όσον αφορά τη σφαιρική λειτουργικότητα των ασθενών με διπολική διαταραχή. Πρέπει ωστόσο να διερευνηθεί η συμβολή και άλλων κλινικών παραμέτρων (συνυπάρχουσες διαταραχές προσωπικότητας, χρήση ουσιών και γενικευμένο άγχος) αλλά και ψυχοκοινωνικών παραγόντων (στίγμα, αυτοστιγματισμός, έλλειψη κοινωνικού δικτύου) στη λειτουργικότητα των ασθενών αυτών.

Λέξεις ευρετηρίου: Κοινωνική λειτουργικότητα, νοητική δυσλειτουργία, Θεωρία του Νου, κοινωνική νόηση, διπολική διαταραχή, ύφεση.

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Research article
Ερευνητική εργασία

The impact of depression and cardiophobia on quality of life in patients with essential hypertension

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Patients with chronic conditions like hypertension may experience many negative emotions which endorse the development of anxiety and depression symptomatology, thus they increase their risk for poor quality of life. Several studies have shown an association between symptoms of psychological distress and hypertension. In this study we aimed to quantify the link between depression, cardiophobia and quality of life in hypertensive patients. A cross-sectional design was employed. A sample of 197 hypertensive patients (89 men–108 women, mean age 53 years, SD=12 ranged 25–78) from a university outpatient hypertension clinic in Greece participated. Ninety-four (47.7%) of the participants suffered from essential grade I hypertension; 68 (34.5%) were grade II; 16 (8.1%) were categorized as grade III, while only 11 (5.6%) patients were recorded as normotensives with high normal values. The questionnaires included: (a) question for the recording of social-demographic characteristics and clinical features, (b) The Short Form (SF-36) Health Survey, (c) The Beck Depression Inventory -I, and (d) The Cardiac Anxiety Questionnaire. There were no significant differences between the two genders with exception of marital status (p=0.010), dyslipidemia (p=0.050), grade of hypertension (p=0.014), cardiac left ventricular hypertrophy (p=0.004), renal failure (p=0.043) and stroke (p=0.024). Lower levels of quality of life and higher levels of depression and cardiophobia were observed compared to the general population. There were no significant differences on psychological measures between the two sexes (p>0.05). Cardiophobia was positively related to depressive symptomatology (r=0.533, p=0.000) while negatively to both

physical and mental health summary measures of SF-36 health survey (r=−0.467, p=0.000 r=−0.537, p=0.000 respectively). Multiple linear regression models found that for psychical health depression and cardiac anxiety, avoidance activities had an influence on levels of quality of life in hypertensive patients, after controlling for age and other socio-demographic variables and clinical characteristics (Beta=−0.133, p=0.007, Beta=−0.364 p=0.000 and Beta=−0.167 p=0.006, respectively). For mental component summary depression and cardiophobia, heart focused attention had also impact on mental health in hypertensives (Beta=−0.438, p=0.016, Beta=−0.564, p=0.000 and Beta=−0.223, p=0.037, respectively) after adjustments. Heart focused anxiety symptoms–as avoidance activities and/or attention and monitoring cardiac activity, are related to hypertensive patients' present deteriorated depressive symptoms and levels of quality of life. Both depressive symptomatology and heart focused anxiety may be a mechanism partly responsible for hypertensive patients' present impaired levels of quality of life.

Key words: Essential hypertension, cardiophobia, depression, heart focused anxiety, psychological distress, quality of life.

Introduction

Essential hypertension represents a major risk factor for cardiovascular and kidney implications (stroke, coronary artery disease, sudden death, end-stage heart and renal failure),[1,2] causing great burden in health systems worldwide since the prevalence of elevated blood pressure in the general population ranges between 30–45% in various registries.[3,4] Emerging evidence further supports the negative impact of arterial hypertension in terms of quality of life.[5,6] Factors leading to this effect have been considered both disease's complications and medication's side effects.[7,8] In addition, low levels of health-related quality of life (HRQOL) implicate the cardiovascular outcome in this group of patients.[9] Hypertensives tend to demonstrate impaired performance in various dimensions of HRQOL as in general well-being, functional capacity and symptoms of psychological distress.[10,11]

There is also a great consideration regarding the role of psychological factors in the cardiovascular spectrum.[12–15] Evidence highlights especially the close link between hypertension and depression, which acts in a reciprocal manner. Depressive mood and anxiety have been associated with higher prevalence of hypertension, whereas clinical diagnosis of depression represents a potential risk factor for the development of high arterial blood pressure.[16–18] Specifically, prospective data show that depressive symptoms enhance the risk of hypertension,[19,20] while other studies reveal that higher levels of blood pressure (BP) are associated with higher incidence of depression.[21,22] Patients under medication for hypertension appear to have even 3-times higher possibility to suffer for major depression.[21] Further evidence enlightens the interference of psychological distress (depressive and anxiety symptomatology) in the former association.[16,17,19,23,24] Patients with uncontrolled high levels of BP tend to demonstrate more stress and depression[24] and otherwise, stress during blood pressure measurements is responsible for white-coat effect as well.[25] Data from the World Mental Health Surveys demonstrate that panic disorder, social phobia and specific phobia were significantly associated with diagnosis of onset hypertension.[26] Some other studies also support that anxiety and depression are strongly correlated with an impaired wellbeing in hypertensive patients.[27]

However, the role of heart focused anxiety (HFA i.e. cardiophobia) with respect to essential hypertension has received less attention. Eifert (1992) defined "HFA as a specific fear of cardiac-related stimuli and sensations because of their expected negative consequences".[28] Persons with cardiophobia and elevated HFA focus attention on their heart when experiencing stress and/or arousal and perceive its function as fundamentally dysregulated.[29] Even if some studies revealed that cardiovascular diseases are associated with health anxiety as well as anxious responding to bodily sensations.[30–32] the identification of cardiophobia as an additional possible factor related to depression and dimensions of HRQOL was not explored in this investigation. Such data merit

attention because they give weight to the relevance of screening for cardiac anxiety symptoms in hypertensive patients in order to try to reduce their negative impact on HRQOL. It is a fact that fear of somatic sensations and symptoms appears to be the basis of many clinical syndromes, such as panic disorders, illness phobias, certain specific phobias, somatization, and pain-related disorders.[31–34]

Therefore in this study we aimed to test a theoretical model that explores the hypothesis whether the association between depressive symptoms and domains of quality of life in hypertensive patients was additionally affected by cardiophobia and heart focused anxiety.

Material and method

Subjects and procedures

We prospectively included 197 newly diagnosed patients with essential hypertension. The patients were recruited from the outpatient hypertension clinic at Hippokration University Hospital of Greece. Further inclusion criteria were: age between 18 and 80 years. Patients had not to be under optimized medical therapy for hypertension before entering the study. All patients underwent a detailed clinical work up including a careful medical history further asking for mental disorders, and additional laboratory testing including blood and urine samples in order to evaluate accompanying cardiovascular risk factors and identify primitive implications of hypertension. Cardiac and carotid ultrasounds were implemented in all participants. Diagnosis of hypertension was established combining office and 24-hour ambulatory blood pressure measurements according to 2007 European Society of Hypertension (ESC)/European Society of Cardiology (ESH) guidelines.[35] Exclusion criteria were as follows: having a psychiatrist disorder or being under relevant treatment for such disorder, secondary hypertension, cognitive impairment, and/or being older than 80 years. All patients gave written informed consent for this study, which was approved by the Ethics Committees of the University of Athens and the Hippokration Hospital. Psychological measures were scored by an expertise psychologist.

Of the 1.307 patients approached during a period of six months, 314 were eligible for inclusion and invited to participate in the study. One hundred and nineteen-seven (62.73%) completed and returned the questionnaires (mean age 53 years, standard deviation SD=12). The rest of them did not complete fully the instruments or did not provide the consent to participate in the study. One hundred-eight (54.8%) patients were females and the rest eighty-nine (45.2%) males. The vast majority of the participants were married (71.1%). The duration of essential hypertension was 27.5 months (SD=40). Ninety-forty of the (47.7%) participants suffered from essential grade I hypertension; 68 (34.5%) were grade II; 16 (8.1%) were categorized as grade III, while only 11 (5.6%) patients were recorded as high normal (normotensives). There were no significant differences between the two genders with exception to marital status (p=0.010), dyslipidemia (p=0.050), grade of hypertension (p=0.014), LV Hypertrophy (p=0.004), renal failure (p=0.043) and stroke (p=0.024). Demographic characteristics of the sample are presented in table 1.

Instruments

Depression

We used the Beck Depression Inventory (BDI-I)[36] in order to measure the depressive symptomatology. The BDI-I is self-report scale consisting of 21-item that assesses cognitive, affective, and somatic depressive symptoms that have occurred over the previous week. This scale although measures depressive symptoms it is not a diagnostic tool to assess major depressive disorder. It has been standardized for the Greek population and has been demonstrated to possess satisfactory psychometric features for clinical and non-clinical samples.[37]

Cardiophobia

Heart focused anxiety (commonly referred to as cardiophobia) was measured using the Greek version of Cardiac Anxiety Questionnaire (CAQ).[38] The CAQ consists of 10 items and 3 subscales: (a) Fear (4 items; e.g, "I worry that I may have a heart attack"); (b) Avoidance (3 items; e.g, "I avoid physical exertion"); and (c) Attention (3 items; e.g, "I can feel my heart in my chest."). The CAQ -10 yields a total score and scores for each above subscale. Values close to 4 are representing more anxiety and cardiac functioning concern (i.e. cardiophobia). It has been standardised for the Greek population and found to possess

Table 1. Study population and descriptive characteristics by gender and total sample.

Variables	Men (n=89)	Women (n=108)	Total (n=197)	Men vs Women
Mean age in years (±SD)	51.5±13.2	54.3±11	53±12	p=0.103
Marital Status				p=0.010
Single	31 (34.8%)	17 (15.7%)	48 (24.4%)	
Married	56 (63.0%)	84 (77.8%)	140 (71.1%)	
Divorced	2 (2.2%)	6 (5.6%)	8 (4.1%)	
Widowed	0 (0.0%)	1 (0.9%)	1 (0.5%)	
COPD				p=0.094
Yes	1 (1.1%)	6 (5.6%)	7 (3.6%)	
No	88 (98.9%)	102 (94.4%)	190 (96.4%)	
Smoking				p=0.356
Yes	37 (41.6%)	52 (48.1%)	89 (45.2%)	
No	52 (58.4%)	56 (51.9%)	108 (54.8%)	
Impaired glucose tolerance				p=0.349
Yes	12 (13.5%)	10 (9.3%)	22 (11.2%)	
No	77 (86.5%)	98 (90.7%)	175 (88.8%)	
Dyslipidemia				
Yes	48 (53.9%)	73 (67.6%)	121 (61.4%)	p=0.050
No	41 (46.1%)	35 (32.4%)	76 (38.6%)	
Duration in mo (mean±SD)	31.5±46	24.7±35.8	27.5±40	p=0.338
Grade Hypertension (n=189)				p=0.014
High normal	2 (2.2%)	9 (8.3%)	11 (5.6%)	
I	35 (39.3%)	59 (54.6%)	94 (47.7%)	
II	37 (41.6%)	31 (28.7%)	68 (34.5%)	
III	11 (12.4%)	5 (4.6%)	16 (8.1%)	
Dipping Status (n=189)				p=0.925
Dippers	56 (62.9%)	70 (64.8%)	126 (64.0%)	
No Dippers	24 (27.0%)	27 (25.0%)	51 (25.9%)	
Reverse Dippers	5 (5.6%)	7 (6.5%)	12 (6.1%)	
CRP (mean±SD)	0.7±1.4	1.1±2	0.9±1.7	p=0.257
Cardiac LV Hypertrophy(n=189)				p=0.004
Yes	42 (47.2%)	30 (27.8%)	72 (36.5%)	
No	43 (48.3%)	74 (68.5%)	117(59.4%)	
Renal Failure (n=189)				p=0.043
Yes	7 (7.9%)	2 (1.9%)	9 (4.6%)	
No	78 (87.6%)	102 (94.4%)	180 (91.3%)	
Stroke (n=189)				p=0.024
Yes	0(0.0%)	6 (5.6%)	6 (3.0%)	
No	85 (95.5%)	98 (90.7%)	183 (92.9%)	
Carotis Intima Media Thickness (n=188)				p=0.067
Yes	32 (36.0%)	26 (24.1%)	58 (29.4%)	
No	53 (59.6%)	77 (71.3%)	130 (66.0%)	

vs=versus, *SD*=Standard Deviation, *COPD*=Chronic Obstructive Pulmonary Disease, *CRP*=C-Reactive Protein, *LV*=Left Ventricular. Note: Missing values exist in various clinical features

satisfactory psychometric features. The stability of the questionnaire was verified by a high test-retest reliability over a 3-mo. period (r=0.86). The test also has high internal consistency (α=0.80).[38]

Quality of life

Quality of life was measured by using the multipurpose health survey Short Form-36 (SF-36) questionnaire. The SF-36 is a self-reported instrument consisting of only 36 questions.[39] It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical (PSC, physical summary component) and mental health summary measures (MSC, mental summary component) and a preference-based health utility index. The score of each dimension is the addition of the item scores of the related dimension further transformed to a score of 0–100. The higher values representing better perceived health-related quality of life.[39] It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. It has been standardized for the Greek population and has been demonstrated to possess satisfactory psychometric features for clinical and non-clinical samples.[40]

Demographic characteristics and clinical features

Along with the measures described above the participants completed a questionnaire regarding socio-demographic information (e.g., age, gender, marital status). Clinical information was recorded and evaluated by a specialist cardiologist doctor during a medical interview at hypertensive unit.

Data analysis

Distributions and descriptive statistics were examined for all variables. The criteria for testing normality were: ≥±2.00 for the Skewness and ≥±5.00 for the Kyrtosis.[41] Relations between quality of life scores and depressive symptoms (BDI) scores and between cardiophobia scales and BDI scores were examined by calculating Pearson correlation coefficients. Multivariate analysis of variance was used to examine links between quality of scores and potential confounding variables: age, marital status, etc as well as links among depressive symptoms. Multiple linear regressions analyses were used to test the potential influence of depression and heart focused anxiety scales on quality of life.

Results

Table 2 provides descriptive results (mean, SD) for the study variables at baseline measurement. Compared to general Greek population (GGP), hypertensive patients demonstrate statistically significant higher scores (p=0.000 to p=0.016) at the scales of depression (8.71±7.02 vs 4.89±5.40 in GGP) fear and anxiety regarding thoracic and heart sensations (1.40±1.04 vs 0.88±0.86 in GGP), total CAQs score (1.10±0.54 vs 0.90±0.60 in GGP), while exhibited significantly lower scores in the various scales of SF-36, such as Role-Physical (78.78±37.20 vs 79.74±37.72 in GGP), Role-Emotional (69.78±36.92 vs 81.53±36.31 in GGP), Vitality (63.00±20.11 vs 66.53±22.39 in GGP), Social Functioning (74.67±18.63 vs 82.05±28.12 in GGP), General Health (56.72±17.43 vs 67.46±23.54 in GGP), Physical Component Summary (71.02±19.03 vs 75.23±29.63 in GGP), and Mental Component Summary (68.48±18.24 vs 74.58±22.02 in GGP). Independent t tests showed that were no significant differences on psychological measures between the two sexes (p>0.05).

Correlations among variables

Cross-sectional results showed that cardiophobia (total CAQ) was positively related to depressive symptomatology (r=0.533, p=0.000) while negatively to both physical and mental health summary measures of SF-36 health survey (r=–0.467, p=0.000 r=–0.537, p=0.000 respectively). Furthermore the dimension of Fear was positively related to depressive symptoms (r=0.378, p=.000) while no significant correlation to both physical and mental health summary measures of HRQOL was observed. Therefore this dimension was not included to the final model. Regarding Avoidance was found positively related to depressive symptomatology (r=0.281, p=0.009) while negatively to physical summary measures of SF-36 health survey (r=–0.444, p=0.000) and therefore we included it only to the final model regarding the dimension of Physical Component Summary (PCS). Finally Attention of cardiac activity was found to correlate positively to current level of depression (r=0.366, p=0.005) and negatively to mental health summary component of SF-36 health survey (r=–0.253,

Table 2. Means and standard deviations for BDI, CAQ and SF-36 scores by sex and whole sample of hypertensive patients compared to General Greek Population.

Variables	Men (n=89)	Women (n=108)	Total (n=197)	Men vs Women	Total vs GGP*
BDI categories				p=0.788	
Minimal Depression (0–13)	70 (78.7%)	50 (46.3%)	120 (60.9%)		
Mild Depression (14–19)	18 (20.2%)	42 (38.9%)	60 (30.5%)		
Moderate Depression (20–28)	1 (1.1%)	14 (13.0)	15 (7.6%)		
Severe Depression (29–63)	0 (0%)	2 (1.9%)	2 (1.0%)		
Total score (mean±SD)	8.28±6.55	9.05±7.37	8.71±7.02	p=0.450	p=0.000
CAQ scores					
Fear	1.27±0.82	1.42±1.18	1.40±1.04	p=0.563	p=0.000
Avoidance	1.06±0.68	1.29±0.93	1.20±0.84	p=0.291	p=0.508
Attention	0.08±0.44	0.68±0.66	0.71±0.58	p=0.399	p=0.699
Total CAQ	1.03±0.32	1.14±0.65	1.10±0.54	p=0.393	p=0.005
SF-36 Health Survey scores					
Physical Functioning(PF)	83.59±36.25	79.62±19.22	81.39±18.55	p=0.143	p=0.639
Role-Physical (RP)	73.52±36.25	68.57±37.98	78.78±37.20	p=0.362	p=0.001
Role-Emotional (RE)	68.24±37.76	71.38±36.35	69.78±36.92	p=0.559	p=0.000
Vitality (VT)	65.71±19.58	56.63±20.15	63.00±20.11	p=0.097	p=0.016
Mental Health (MH)	68.76±17.25	64.04±19.50	66.13±18.63	p=0.081	p=0.120
Social Functioning (SF)	75.88±23.28	73.71±16.43	74.67±18.63	p=0.538	p=0.000
Bodily Pain (BP)	75.26±24.74	76.09±24.26	75.72±24.42	p=0.815	p=0.120
General Health (GH)	58.47±18.02	55.32±16.90	56.72±17.43	p=0.214	p=0.000
Physical Component Summary (PCS)	72.25±19.27	67.55±20.56	71.02±19.03	p=0.419	P=0.002
Mental Component Summary (MCS)	69.65±19.24	68.79±18.44	68.48±18.24	p=0.472	p=0.000

**GGP*=General Health Population, *BDI*=Beck Depression Inventory, *CAQ*=Cardiac Anxiety Questionnaire, *SF-36*= Short Form-36

p=0.009). As a result we included this dimension of cardiophobia only to the final model regarding the dimension of MCS. The correlations for the psychological variables after controlling for age and gender are presented in table 3.

Potential influence of demographic characteristics and clinical features

Furthermore, in order to clarify the potential influence of demographic and clinical information on the relationship among the two summary components of HRQOL, depressive symptomatology and cardiophobia, we performed multivariate analysis of variance. The results showed significant associations for marital status on MCS SF-36 and, for chronic obstructive pulmonary disease (COPD) on BDI and for the duration of hypertension on PCS. Therefore, these factors were included in the final model testing the role of depression and cardiophobia on quality of life. Detailed associations between variables are presented in table 4.

Testing the impact of depression and cardiophobia on quality of life

Tables 5 and 6 present the results of two multiple regression models, testing the potential link between depression, cardiophobia and quality of life in hypertensive patients. All analyses were con-

Table 3. Pearson correlations of depression, cardiophobia (Total CAQ and dimensions) and quality of life by total sample after controlling for age and gender.

	1	2	3	4	5	6	7
Variables							
SF-36 PCS	1						
SF-36 MCS	0.725***	1					
BDI	–0.452***	–0.616***	1				
Fear CAQ	–0.109	–0.226	0.378***	1			
Avoidance CAQ	–0.444***	–0.190	0.281**	0.406***	1		
Attention CAQ	–0.185	–0.253**	0.366**	0.464***	0.485***	1	
Total CAQ	–0.467***	–0.537***	0.533***	0.746***	0.633***	0.519***	1

***p<0.001, **p<0.01, *p<0.05, *BDI*=Beck Depression Inventory, *CAQ*=Cardiac Anxiety Questionnaire, SF-36=Short Form-36, *PCS*=Physical Component Summary, *MCS*=Mental Component Summary

Table 4. Potential influence of demographic characteristics and clinical features in quality of life, depressive symptoms and cardiophobia.

Variables	SF-36 PCS (p)	SF-36 MCS (p)	BDI Total (p)	CAQ Total (p)
Age	0.374	0.820	0.747	0.180
Gender	0.419	0.472	0.450	0.495
Marital Status	0.883	0.020	0.195	0.147
COPD	0.345	0.258	0.019	0.176
Smoking	0.336	0.920	0.258	0.671
Diabetes	0.752	0.506	0.785	0.736
Dyslipidemia	0.081	0.115	0.647	0.636
Duration	0.020	0.059	0.564	0.239
Hypertension Grade	0.574	0.943	0.093	0.324
Dipping Status	0.428	0.894	0.218	0.112
Peak SBP	0.903	0.753	0.713	0.747
Peak DBP	0.869	0.570	0.815	0.689
CRP	0.691	0.156	0.357	0.326
Renal Failure	0.808	0.133	0.592	0.446
Stroke	0.582	0.346	0.356	0.758

COPD=Chronic Obstructive Pulmonary Disease, *SBP*=Systolic Blood Pressure, *DBP*=Diastolic Blood Pressure, *CRP*=C-reactive protein

ducted separately for physical (PSC) and for mental (MSC) components of SF-36. Though age didn't show significant correlations with regard to multivariate testing, we decided to include this factor in the final regression models as there are relevant published data to support their effect on quality of life. On the whole, multiple regression models found that for psychical health both depression and cardiophobia affect the levels of quality of life in hypertensive patients after controlling for age and other socio-demographic variables (Beta=–0.133, p=0.007, Beta=–0.364, p=0.000 respectively). For mental component summary both depression and cardiophobia had also impact on mental health in hypertensives (Beta=–0.438, p=0.016 and Beta=–0.564, p=0.000) after adjustments. To sum up, adequate associations remain for depression and cardiophobia in both models.

Table 5. Multiple regression models for PCS-36.

Model		R Square	Beta	t	p
1	(constant)			8.750	0.000
	Age	53.1%	–0.136 d	–0.796	0.432
	Marital Status		0.215 d	1.145	0.065
	Hypertension Grade		0.114 d	1.092	0.060
	COPD		0.182 d	1.183	0.247
	Duration		–0.257	–3.030	0.005
	Depression		–0.133	–2.702	0.007
	Cardiophobia (Total CAQ)		–0.364	–5.854	0.000
	Avoidance (CAQ)		–0.167	–2.961	0.006
	a. Independent variable: SF36-PCS				

1=Enter, *COPD*=Chronic Obstructive Pulmonary Disease, *CAQ*=Cardiac Anxiety Questionnaire, *PCS-36*=Short Form-36 Physical Component Summary

Table 6. Multiple regression models for MCS-36.

Model		R Square	Beta	t	p
1	(constant)			6.750	0.000
	Age	60.5%	–0.091 d	–0.576	0.570
	Marital Status		0.302 d	1.973	0.059
	Hypertension Grade		0.058 d	0.422	0.676
	COPD		–0.096 d	–0.676	0.505
	Duration		–0.375	–2.709	0.012
	Depression		–0.438	–2.573	0.016
	Cardiophobia (Total CAQ)		–0.564	–5.854	0.000
	Heart Focused Attention (CAQ)		–0.223	–2.110	0.037
	a. Independent variable: SF36-MCS				

1=Enter, *COPD*=Chronic Obstructive Pulmonary Disease, *CAQ*=Cardiac Anxiety Questionnaire, *MCS-36*=Short Form-36 Mental Component Summary

Discussion

In this study we explored the possible affecting role of depression and cardiophobia, on HRQOL in essential hypertension era. We found that hypertensive patients demonstrated higher scores in terms of depression and cardiac focus anxiety, whereas presented decreased scores in quality of life, compared to general population. These differences remained significant regardless age, gender variations or other social-demographic and clinical features, which is in contrast with previous published studies.[23,42–44] The existing data also indicated the role of duration of hypertension in patient's quality of life, which was a finding recurred in this particular survey.[44,45] When we performed multiple regression models to test the impact of different factors on HRQOL, depression and cardiophobia were found significantly to affect the quality of life of hypertensive patients.

Our findings are in line with the vast majority of studies punctuate the strong bidirectional link between depression and hypertension.[16–25] Most of the dimensions of hypertensive patients' quality of life also were found impaired in our sample as it was expected according to recent evidence.[5–8,10,11] Our study further gives some support on the association between depressive symptoms and general well being, as it is calculated by HRQOL general instruments;

a theoretical construct for which only scarce published data exist.[27,42,44] We have also showed that in the context of essential hypertension both depressive mood and symptoms of psychological distress, expressed by heart focused anxiety measurements, are responsible for over 50% of the physical component and almost 60% of the mental component of hypertensive patient's feeling of decreased well being. Thus this correlation partly influenced from other social-demographic or clinical determinants, except of marital status and duration of the hypertensive disease. Of course, due to the small impact of beta coefficients, these results must be considered with caution.

We performed a comprehensive clinical and laboratory investigation in our clinical sample, in order to define cardiovascular risk factors, crucial co-morbidities and primary (left ventricular hypertrophy, carotid intima media thickness etc) or established target organ damages (renal/heart failure , stroke etc). Nevertheless, all these factors unexpectedly had a minor and –according to our investigation– non significant contribution to quality of life context. A longitudinal clinical history of hypertension seems solely to affect patient's feeling of inadequate personal health.[44,45] It is reasonable to assume that a long history of elevated BP simply reinforces the effect of factors of psychological distress. Our data revealed that being in a situation of high BP measurements for a long period of time creates a psychological stressful basis with an effect in patient's life quality. The latter is supported from existing evidence.[46,47]

In this study, we principally aimed to explore the pathway leading from depression and anxiety to quality of life. To be more specific, besides depression and total heart focused anxiety, as for the physical component summary of quality of life, we found that avoidance of actions related to stressed cardiac function i.e. activities elevating BP, heart rate etc. is an extra factor of lower levels of quality of life. On the other hand, as far as for the mental component of quality of life, it seems to be partly influenced especially by attention, which means these patients express a behavior controlled by thorough cardiac monitoring (checking constantly heart pulse, worrying for palpitations, regular BP measurements etc.). We should point out that the former connection acts reciprocally and such distressed behaviors, characterized by factors like attention and avoidance combined with a prolonged history of hypertension further enforce depressive symptomatology. Previous evidence enlightens the link of elevated BP with increased stress and anxiety, in respect with increased sympathetic activity.[13,48]

This study contains some caveats, worthy to refer. First, the cross-sectional design limits any assumption about possible causal associations between the various factors. The selection of the sample further was much dependant to patient's consent to participate in this study. It is plausible to hypothesize those subjects with more prominent symptoms of distress or having great burden of hypertension or accompanying co-morbidities excluded from the final analysis.[43] For instance, the proportion of Grade III hypertension in our sample was small, so the possible effect of more strained clinical syndrome on quality of life may be down-regulated.[44,45] Moreover, our results were obtained through baseline evaluations during the first visit in an outpatient hypertension clinic. It could be essential to speculate that the observed correlations could be affected in follow-up measurements. However, published data support that these psychological factors demonstrate minor influences even in more prospective approaches.[43,45] We performed initial follow up evaluations in a subgroup of our population and we didn't find significant changes during time.* Our research design additionally minimizes the possible effect of other confounding factors as implemented medication.[49,50] Nevertheless, it could be useful to explore our hypothesis in multiple time points to establish more solid evidence.

To sum up, this study possibly provides a satisfactory explanation of how psychological distress mapping the road from essential hypertension to impaired HRQOL. Taking in consider the limitations, we illustrate a novel insight in the understanding the etiology of hypertension focused on its possible psychosomatic nature, at least for mild grade I and II essential hypertension.

* These data are available upon request

Η επίδραση της κατάθλιψης και της καρδιοφοβίας στην ποιότητα ζωής των ασθενών με ιδιοπαθή υπέρταση

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Ασθενείς με χρόνιες καταστάσεις όπως η υπέρταση συχνά βιώνουν αρνητικά συναισθήματα, τα οποία ευνοούν την ανάπτυξη αγχώδους και καταθλιπτικής συμπτωματολογίας και αυξάνουν τον κίνδυνο για επηρεασμένη ποιότητα ζωής. Αρκετές μελέτες υποστηρίζουν αυτή τη συσχέτιση ανάμεσα στις καταστάσεις ψυχολογικού στρες και την υπέρταση. Στην παρούσα συγχρονική εργασία επιδιώξαμε να ποσοτικοποιήσουμε τον σύνδεσμο ανάμεσα στην κατάθλιψη, στην καρδιοφοβία και στην ποιότητα ζωής στους υπερτασικούς ασθενείς. Το δείγμα μας ήταν 197 ασθενείς με ιδιοπαθή υπέρταση (89 άνδρες, 108 γυναίκες, μέση ηλικία 53 χρόνια, σταθερή απόκλιση=12 χρόνια, εύρος 25–78) προερχόμενοι από το αντιυπερτασικό ιατρείο ενός πανεπιστημιακού νοσοκομείου των Αθηνών. Ενενήντα τέσσερεις ασθενείς (47,7%) είχαν υπέρταση σταδίου Ι, 68 (34,5%) είχαν υπέρταση σταδίου ΙΙ, 16 (8,1%) κατηγοριοποιήθηκαν ως σταδίου ΙΙΙ, ενώ μόνο 11 (5,6%) συμμετέχοντες καταγράφηκαν ως νορμοτασικοί με υψηλές φυσιολογικές τιμές αρτηριακής πίεσης. Τα εργαλεία που χρησιμοποιήθηκαν ήταν: (α) ερωτηματολόγιο κοινωνικο-δημογραφικών χαρακτηριστικών και κλινικών παραμέτρων, (β) η Επισκόπηση Υγείας SF-36, (γ) η Κλίμακα Κατάθλιψης του Beck, και (δ) η Κλίμακα Μέτρησης Άγχους για την Καρδιακή Λειτουργία. Δεν υπήρχαν στατιστικά σημαντικές διαφορές ανάμεσα στα δύο φύλα εκτός από την οικογενειακή κατάσταση (p=0,010), τη δυσλιπιδαιμία (p=0,050), το στάδιο της υπέρτασης (p=0,014), τον δείκτη υπερτροφίας της αριστερής κοιλίας της καρδιάς (p=0,004), τη νεφρική ανεπάρκεια, (p=0,043) και το ιστορικό εγκεφαλικού επεισοδίου (p=0,024). Γενικά παρατηρήθηκαν χαμηλά επίπεδα ποιότητας ζωής και υψηλά επίπεδα καταθλιπτικής συμπτωματολογίας και καρδιοφοβίας στους ασθενείς με υπέρταση σε σύγκριση με τον γενικό πληθυσμό. Η κατά φύλο σύγκριση δεν ανέδειξε στατιστικά σημαντικές διαφορές (p>0,05). Διαπιστώθηκε ότι η καρδιοφοβία σχετίζεται θετικά με την καταθλιπτική συμπτωματολογία (r=0,533, p=0,000) και αρνητικά τόσο με τη σωματική όσο και με την ψυχική διάσταση της Επισκόπησης της Υγείας SF-36 (r=–0,467, p=0,000 r=–0,537, p=0,000 αντιστοίχως). Η ανάλυση πολλαπλής γραμμικής παλινδρόμησης έδειξε ότι η κατάθλιψη, το άγχος για την καρδιακή λειτουργία και οι δραστηριότητες αποφυγής φαίνεται να έχουν επίδραση στα επίπεδα της σωματικής διάστασης της ποιότητας ζωής των υπερτασικών ασθενών, μετά από στάθμιση για τους διάφορους κοινωνικο-δημογραφικούς παράγοντες και κλινικές παραμέτρους (Beta=–0,133, p=0,007, Beta=–0,364 p=0,000 και Beta=–0,167 p=0,006, αντιστοίχως). Από την άλλη πλευρά η κατάθλιψη, η καρδιοφοβία και η επικέντρωση στην καρδιακή λειτουργία είναι οι κύριοι παράγοντες που επηρεάζουν την ψυχική διάσταση της ποιότητας ζωής των υπερτασικών (Beta=–0,438, p=0,016, Beta=–0,564, p=0,000 και Beta=–0,223, p=0,037, αντιστοίχως). Τελικά οι διαστάσεις του άγχους για την καρδιακή λειτουργία, όπως η επικέντρωση στην καρδιακή λειτουργία και η αποφυγή δραστηριοτήτων που δυνητικά την επιβαρύνουν, φαίνεται να σχετίζονται με την καταθλιπτική συμπτωματολογία και τα επίπεδα της ποιότητας ζωής των υπερτασικών ασθενών. Πιθανώς η καταθλιπτική συμπτωματολογία σε συνδυασμό με την καρδιοφοβία να αποτελούν μέρος του μηχανισμού που είναι υπεύθυνος για την επηρεασμένη ποιότητα ζωής στην ιδιοπαθή υπέρταση.

Λέξεις ευρετηρίου: Ιδιοπαθής υπέρταση, καρδιοφοβία, κατάθλιψη, άγχος για την καρδιακή λειτουργία, ψυχολογική δυσφορία, ποιότητα ζωής.

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Review article
Ανασκόπηση

There is no safe threshold for lead exposure: A literature review

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Lead was one of the most dangerous environmental toxic substances for a long time in western countries, and this is still the case for many places on earth today. Its neurotoxic potential is highly significant but its secure blood level concentration remains unknown. The aim of this study was to approach the above issue from the perspective of social psychiatry. A systematic search was made of Dialog and Datastar interfaces for data regarding the neuropsychiatric complications of direct or chronic exposure to lead, and a review of the relevant literature was conducted using the databases Medline, Embase, CAB Global Health and Cochrane. Lead affects the cholinergic, dopaminergic and gloutamergic systems, thus intervening in the normal function of neurotransmion. The consequence of neurotoxicity in the central nervous system includes apoptosis and excitotoxicity. Direct as well as chronic exposure causes serious neurological symptoms and possibly constant cognitive impairment. Acute encephalopathy, the most serious expression of lead poisoning, occurs in blood level concentrations over 100 μg/dL in adults and 80–100 μg/dL in children. Early symptoms of lead neurotoxicity include irritability, headaches and difficulties in concentration in both children and adults. Continuous exposure in children produces neurobehavioral symptoms, such as decreased concentration, inability to follow instructions, difficulty to play games and low IQ, which are associated with concentrations of 10–35 μg/dL. However, some studies claim that cognitive decline and low IQ can occur in concentrations <10 μg/dL. The commonest symptom in adults is peripheral neuropathy with foot drop. Prenatal exposure to lead has been correlated with antisocial behavior and schizophrenia. Long-term lead exposure causing low and medium lead concentration in blood has been linked to depression as well as generalized anxiety disorder and other behavioral disorders. High blood level concentrations correlate with psychotic symptoms like delusions and hallucinations but more rarely with psychotic syndromes. Despite the fact that lead has been banned from gasoline, paint and water pipes, quite significant quantities of lead still exist, particularly in deprived areas of modern cities, in transition zones and city centers,

and there are also great concentrations around lead mines and in developing countries, but even for the remaining areas there is no safe threshold. CONCLUSIONS: Lead was and still is an environmental factor that increases neurologic and psychiatric morbidity. It also causes developmental disorders, especially in deprived areas. Prevention should be the single most important way of dealing with lead poisoning.

Key words: Lead, exposure, neurotoxicity, safe threshold.

Introduction

Lead is a well known neurotoxicant that causes a variety of clinical conditions. Recent data now indicate that low level exposure (blood lead levels below 10 μg/dL) results in cognitive dysfunction, neurobehavioral disorders, neurological damage, hypertension and renal impairment.[1] Exposure to heavy metals early in development can predispose the brain to develop a neurodegenerative disease later in life. Alternatively, lead can exert their adverse effects through acute neurotoxicity or through slow accumulation during prolonged periods of life.[2] Inorganic and organic forms of lead are absorbed mainly by ingestion and inhalation; organic compounds may also be absorbed through the skin[3] and can cross the placental barrier.[4,5] In occupational settings, exposure through inhalation is more common, whereas in the general population it is largely through ingestion.[6]

Exposure, absorption and distribution

Exposure to lead has been known to be neurotoxic since Roman times.[7] The removal of lead from paint in the 1970s and leaded gasoline in 1990 resulted in substantial lowering of mean blood lead levels. Between 1976 and 1991, levels fell from 15.8 to 2.8 μg/dL in adults and 13.7 μg/dL to 3.2 μg/dL in children.[8,9] Nowadays, common sources of lead exposure are lead-based paint in old houses, contaminated soil, household dust, old water pipes and lead-glazed ceramics.[10] Children are more susceptible to lead toxicity than adults, due to particular exposure pathways via hand-to-mouth activities like pica,[11,12] and because they have a developing system of cell differentiation and growth that is more vulnerable to inhibition and damage.[13]

It has been determined that lead can cross the placenta with fetal uptake beginning at 12 weeks of gestation and continuing up to birth. In fact, pregnant women with high blood lead levels may not display the toxic effects of lead poisoning, yet the development of the fetus can still be damaged in any trimester.[14–16]

Mechanisms of lead neurotoxicity

Lead can affect the nervous system by multiple mechanisms, an important one of which competes with or mimics the action of calcium (influx) in neuron cells due to the chemical similarity. This disturbs calcium entry into cells and alters mitochondrial structure, leading to inhibited cellular respiration and altered calcium-based reactions and neuronal signalling.[17,18]

Calcium is the natural physiologic activator of Protein Kinase C (PCK), but the ability of lead to substitute calcium in the activation of PCK can lead to the impairment of brain microvascular formation and function, while high levels of lead exposure may disrupt the blood-brain barrier.[19,20] Excessive PCK activation can disrupt prefrontal cortical regulation of behavior and thought, possibly contributing to signs of prefrontal cortical dysfunction such as distractibility, impaired judgment and thought disorder.[21]

Lead also affects the glutamatergic, cholinergic and dopaminergic systems.[22] Most of the evidence available suggests that lead interferes with glutamate, which is critical for learning in the developing brain, by acting as an antagonist with its receptor (N-Methyl-D-Aspartate receptor-NMDAr).[23] It may also impair the regulation of dopamine synthesis and release, block evoked release of acetylcholine and decrease cholinergic function, and interfere

with γ-Amino Butiric Acid (GABA) neurotransmission by heme synthesis inhibition.[24] Furthermore, lead affects the levels and metabolism of serotonin[25] and the hypothalamic-pituitary-adrenal (HPA) axis which can lead to permanent HPA axis dysfunction.[26]

Lead can also cause neurotoxicity by increasing free radicals or by direct depletion of antioxidant reserves such as glutathione.[27] Lead-related oxidative stress can result in increased neuron vulnerability, activating the apoptosis program and inducing excitotoxicity, notably for astrocytes and microglia.

The dose-effect relationship of lead toxicity in the human brain seems to be associated with low level exposure in a biphasic pattern. Hence, in low blood lead level concentrations, it seems that there is a suppression of the glutamatergic system not seen in higher concentrations but which reappears in even higher concentrations following a pattern of reversed U.

Cecil[28] showed that a higher mean childhood blood lead concentration is related to region-specific reductions in adult gray matter volume, especially in the anterior cingulate cortex, which may affect mood regulation. Bellinger[29] confirmed that the greater lead-associated neurocognitive and behavioral findings in males suggest an underlying physiologic difference in how the brains of men and women respond to childhood lead exposure. The authors agree with previous studies suggesting that volume loss in both the cognitive and emotional territories of anterior cingulate cortex can explain the behavioral and cognitive problems with lead exposure. Bellinger observed that childhood lead exposure is associated with a significant and persistent impact on white matter microstructure.

Neurologic and neurocognitive implications of lead intoxication

The toxic effects of lead vary greatly, ranging from potentially fatal encephalopathy in acute lead poisoning to subtle changes in neurocognitive function at low level exposure. As exposure progresses, symptoms may manifest differently.[30]

Brain damage (encephalopathy) is common at high exposure (blood levels above 100–120 μg/dL for adults and 80–100 μg/dL in children) and can be fatal or permanently disabling, resulting in dementia.[31,32]

Chronic exposure to high lead concentration induces cognitive deficits in the domains of viso-spatial perception, attention, recognition memory and new learning as well as neurological impairment such as gait ataxia, dysdiachokinesia and increased tendon reflexes, and can also lead to toxic encephalopathy.[33,34]

Moderate blood lead levels between 20–70 μg/100 mL can cause cognitive impairment as well as mood and behavioural disorders and other physical symptoms like anorexia, intermittent vomiting, abdominal pain, peripheral neuropathy with the characteristic foot drop, and lethargy. Results of more recent cross-sectional and prospective studies indicate that postnatal lead exposure resulting in blood levels as low as 25 μg/dL, and probably lower, are also associated with deficits in intellectual attainment and affect behavior.[35]

Baker reported various neurobehavioral effects in workers with blood lead concentrations between 40 and 60 micrograms/100 mL showing impaired performance in tests of verbal concept formation, visual/motor performance, memory, and mood. Furthermore, this impairment occurred in the absence of peripheral nervous system derangement and increased in severity with increasing lead concentrations.[36] Similar results were obtained by other studies that associated lead exposure with subclinical decrements of neurocognitive function.[37–39]

In the population-based sample of adults 20–59 years of age participating in the National Health and Nutrition Examination Survey III (NHANES III) study, no relationship was found between blood lead concentration (geometric mean 2,51 μg/dL) and covariate-adjusted performance assessment of neurocognitive function. However, significant associations have emerged in some studies involving older adults with slightly higher blood lead concentrations. A recent study with 991 participants,

which sought to determine whether long-term exposure to high levels of lead in the environment is associated with decrements in cognitive ability in older Americans, concluded that permanent cognitive decline is an effect of cumulative lead dose following previous environmental exposure and also that a portion of age-related decrements in cognitive function in this population might be associated with earlier lead exposure.[40] Wright[41] studied the association of lead exposure biomarkers with cognitive test scores as well as the modifying effects of age on the lead cognition relationship, and found that lead exposure might accelerate age-associated cognitive decline.

However, a meta-analysis of occupational studies by Goodman[42] suggested that none of the individual studies is adequate or conclusive in providing information on the subclinical neurobehavioral effects of lead exposure. Additionally, the authors claim that the studies do not provide adequate data for drawing firm conclusions about the biological effects of current lead exposure.

Effect in children

The levels of lead considered tolerable for children have been repeatedly lowered over the past three decades. In the early 1960s, the toxic threshold was established as blood lead levels of 60 μg/dL.[43] In 1970, the threshold was reduced to 40 μg/dL;[44] it was further reduced to 30 μg/dL in 1975 and again to 25 μg/dL in 1985.

Finally, in 1991, CDC set the international level at 10 μg/dL.[45] According to Bellinger,[46] although this level only intends to serve as a risk guidance and management tool, it has been widely and incorrectly imbued with biological significance for the individual child. Indeed, the intervention level is often interpreted as a threshold; thus, a level lower than 10 μg/dL would be considered "safe," and a higher level "toxic." There is no safe level of lead exposure given that factors such as the endpoint of interest, age at exposure and at assessment, duration of blood lead elevation, and the characteristics of the child's rearing environment must also be considered.

Children are particularly vulnerable to lead poisoning. Some argue that the most detrimental effect of lead in children is neurotoxicity within the CNS.[47] Mild and moderate lead levels can also cause cognitive and behavioral problems. For each 10 μgr/dL increase in blood lead level, cognitive test scores decrease by 3.2 points.[48] Usually the effects are long-term and affect IQ scores, developmental delays, learning disabilities and other neurocognitive and behavioral effects.[49,50] The outcomes of four key studies of the neurobehavioral effects of low-level lead exposure in children were reviewed and analyzed by Davis[51] who concluded that blood lead levels of 10–15 μg/dL can cause impaired neurobehavioral activity. The results of a study involving 246 inner city young Afro-American children with a mean age of 7.5 years showed neurobehavioral deficits in areas of intelligence, reaction time, visual-motor integration, fine motor skills and attention, including executive function at levels <10 μg/dL.[52]

Blood lead levels above 10 μg/dL have been reliably associated with Attention Deficit Hyperactivity Disorder (ADHD), with the only real dispute being the magnitude of the effect.[53–55] Lead exposure is a plausible neurobiological candidate for ADHD involvement because it disrupts midbrain dopamine and other neurotransmission circuitry,[56] systems that are also implicated in ADHD.[57]

In a cross-sectional study of 756 children with a mean blood lead level of 11.4 μg/dL, Roy et al[58] noted that lead exposure affected behavior across multiple domains, including anxiety and social behavior. Their results also suggested that executive functions and attention are especially vulnerable to insult by lead among young children. They also observed that children with higher blood lead levels presented with more ADHD-type behaviors, especially the inattention component. However, it is not clear if behavioral changes precede lead exposure and could even induce lead exposure through behavioral pathways such as increased hand-to-mouth behavior. In contrast, Nigg et al[59] reported that even very low levels of blood lead exposure (<5 μg/dL) were associated with ADHD. They con-

firmed their previous findings and concluded that when applying DSM-IV ratings, blood lead was found to be reliably associated with hyperactivity but not inattention.

Furthermore, other studies suggested cognitive and behavioral deficits in children related to low and very low lead exposure. In prospective studies, it has been found that lead exposure in early life can cause neurocognitive deficits with no low-dose threshold.[60] The NHANES III findings lead to the conclusion that deficits in cognitive and academic skills associated with lead exposure occur at blood lead concentrations of less than 5 μg/dL.[61] However, there is some skepticism about the methodology of this study due to the fact that these findings proved difficult to be replicated.[62]

Latest studies also suggested that although the developing brain is vulnerable to the neurotoxic effects of lead, it is difficult to understand the exact correlation of lead neurotoxicity in infants, even in the case of lead exposure.[63]

Psychiatric implications of lead poisoning

Despite the detailed knowledge regarding the effects of lead poisoning on neurocognition, there is significantly less and vague evidence in terms of psychiatric complications.

In a prospective study conducted in Cincinnati, prenatal and average childhood blood lead concentrations were reported to be associated with a greater risk of delinquent behavior later in life.[64] Prenatal lead exposure may increase the risk of other psychiatric disorders. The behavioral deficits associated with lead exposure strongly resemble certain premorbid features of schizophrenia, such as reduced attention and neurocognitive impairment. Opler[65] conducted a study of prenatal lead exposure and schizophrenia in 2004, using δ-aminolevulinic acid from maternal serum as an indirect biologic marker of lead exposure. The findings suggested a possible association of prenatal lead exposure and the development of adult-onset schizophrenia. In a second study in 2008 by the same group, the results provided further evidence for the role of early environmental exposure in the development of adult-onset psychiatric disorders.[66]

Using logistic regression models adjusted for age, alcohol intake, employment status, and education status, Rhodes et al found that long-term exposure is associated with depression, stress and behavioral symptoms.[67] The analysis of hair samples taken from ten symptomatic bipolar patients and from ten normal controls matched for age, sex and race suggested that a relatively high body lead burden may be associated with manic episodes of bipolar illness.[68]

In a cross-sectional epidemiologic survey, Bouchard[69] used NHANES data from 1999 to 2004 to investigate the relation between blood lead levels and the odds of major depressive disorder (MDD), panic disorder (PD) and generalized anxiety disorder (GAD) in a sample of US population aged 20 to 39 years. Increased blood lead levels were associated with a significantly higher risk of MD and PD in young adults with low levels of lead exposure but not GAD.

Stanley and Wakwe[70] measured serum lead levels in 21 depressive, 20 manic-depressive and 20 schizophrenic in-and outpatients of a mental health unit. Lead was found to be increased in depressives ($p<0.01$) and schizophrenics ($p<0.05$) but not in mania patients.

In contrast, a cross-sectional study by Golub et al[71] did not demonstrate a consistent association between environmental lead exposure and depression within the investigated blood lead levels. While their study found a statistically significant association between blood lead level and depression, when exposure was modeled as a categorical variable and only age, gender and sex were considered, the effect was small with a relative risk around 1.3. In addition, when education level and poverty income ratio were added to the model, no clear trends emerged to show that the risk of depression increases with the increase in blood lead levels. The authors underline the importance of considering the effects of socio-economic measures, such as education and poverty income ra-

tio in the investigation of lead effects on health. Longitudinal studies will be necessary to examine more fully the effect of environmental lead exposure on depression, including measures of HPA axis function, to help elucidate potential biological mechanisms.

Higher levels of lead concentrations are associated with psychotic symptoms such as hallucinations or delusions and more rarely with psychotic syndromes.

Rajan[72] evaluated the association between lead burden and psychiatric symptoms and its potential modification by genetic polymorphism in a longitudinal study with 1,075 elderly male participants. Increased lead burden was significantly associated with increased somatization, hostility and global distress. Participants with the allele 1-1 Aminolevulinic Acid Dehydrate (ALAD 1-1) genotype appeared to be at greater risk, particularly with regard to phobic anxiety symptoms, than those participants who were carriers of at least one variant ALAD allele.

Condray[73] investigated the relationship between chronic solvent exposure and adult lifetime psychiatric disorders as well as the relationship between solvent exposure and personality changes. In this study, 29 male painters and 32 male non-painter control subjects underwent semi-structured diagnostic interviews for DSM-III-R Axis I and Axis II disorders. Results showed that the probability of being diagnosed with a mood disorder differed significantly between painters (41%) and control subjects (16%). The groups did not differ in regard to personality disorders involving an onset before 25 years of age. In contrast, painters exhibited a subclinical pattern of personality dysfunction involving symptomatology and particularly increased difficulties in the domains of interpersonal relationships and impulse control that was measured allowing for onset after the age 25. Finally, a significant dose-response relationship was observed between career solvent exposure, blood lead level, and personality symptoms. These data showed an increased rate of psychological disturbance in a significant and substantial number of painters. However, not all painters were so characterized. This latter pattern raises the question of the potential role of differential vulnerability. ALAD-1 allele is also suggested as being partly responsible for this phenomenon.

Despite the above evidence, mainly deriving from epidemiological studies, no clear cause-effect relationship between lead poisoning and psychiatric symptoms has been established. Clinical improvement after lead burden reduction treatment can be helpful in providing some evidence regarding a potential relationship, although it is moderately effective as single treatment in the majority of reported cases.

An older study, regarding 1,113 autistic or hyperactive children with a mean blood lead value of 15.6 mgc following a program to reduce lead burden, resulted in clinical improvement of their symptoms.[74] In another study, Dimercaptosuccinic Acid (DMSA) was used to diminish the body burden of lead in clinically depressed patients after chronic lead exposure; few cases of documented clinical improvement following treatment have been reported. One case, involving a long-term lead worker with moderate to severe depression, appeared to respond dramatically to DMSA.[75] In another case study, a 52-year old male artisan of stained glass was admitted to hospital for depression twice, with one suicidal attempt and without neurological symptoms, cognitive or memory problems. His depression was lifted once the body burden of lead was reduced.[76]

Although there is strong evidence that lead burden can be related to anxiety, depressive and behavioral symptoms, the degree to which psychiatric symptoms cluster together to constitute psychiatric syndromes is not certain. Furthermore, most studies suggest that individual vulnerability due to genetic, socio-economic or other confounding factors must be considered before drawing any certain conclusions. Bouchard et al suggest that when assessing the role of lead as a risk factor for mental health outcomes, an indicator of long-term lead exposure, such as bone lead level, is desirable. Bone lead level has a clearance half-life of years to decades.

As a general conclusion, it is worth considering lead exposure as an occupational or environmental hazard during the psychiatric interview, especially when anxiety, behavioral or depressive symptoms are apparent.

Prevention

Prevention of lead poisoning, other than the obvious social benefit, can also prove cost-effective and can be accomplished with the implementation of policies aimed to control possible sources of lead in the environment, and/or with educational programs that place the burden of preventing exposure on the individual and the family. Phasing out lead from gasoline, paint and food containers has been highly effective in reducing average lead exposure, but racial and income disparities persist. Although enforcement and lead abatement have been shown to reduce the societal cost of lead exposure within the home, dust control has limited efficacy.[77] Surveys conducted to examine whether pamphlets can increase the awareness of lead preventive techniques have shown mixed results.[78,79] Similar results were obtained by Polivka[80] who found it difficult to raise the awareness in people with low income and low education. People in poor areas tend to suffer more often from mental health problems, mainly depression, which makes it more difficult to implement lead exposure prevention programs either for them or their children.[81] According to DeSilva,[82] the intellectual deficits caused by lead exposure promote behaviors that increase the exposure itself. Nevin[83] also found that violent crime rates, rates of pregnancy at the age of 15 or less and unwed pregnancies are related to societal lead exposure over the last 50 years.

Medical treatment of individuals with overt lead intoxication involves decontamination, supportive care and judicious use of chelating agents.[84] A variety of chelating agents have been demonstrated to decrease blood lead concentrations. A recent clinical trial of oral chelation in young children with blood lead concentrations raging from 22 to 44 μg/dL found that the drug succimer lowered blood concentrations transiently but did not improve cognitive function.[85,86] Although in some instances chelation therapy has proved effective in improving depressive symptoms and more rarely in treating depressive episodes, and anecdotal evidence suggests that chelation has been associated with improvement in symptoms and decreased mortality in patients with lead encephalopathy, controlled clinical trials demonstrating efficacy are lacking.[87,88]

Despite the available chelation treatment or other alternatives to reduce body lead burden, primary prevention will be the most important technique in the future for eliminating lead poisoning.

Conclusions

Lead neurotoxicity may be a contributing factor for adverse mental health outcomes, even at levels generally considered to pose no risk. Studies continue to describe apparent effects that were previously unknown and show that these effects can be detected at increasingly lower levels of exposure.

The well-known pharmacokinetics of lead in the nervous system combined with the epidemiological data mentioned above are in accordance with recent theories regarding schizophrenia.[89]

These data rate lead exposure as a severe environmental hazard that needs to be addressed through health policies and also to be taken into account in the differential diagnosis of neurological and mental health disorders.

The implementation of measures concerning lead poisoning prevention within the home lies mainly in the hands of individuals, despite various national policies. Awareness must be raised regarding lead poisoning and related protective techniques, especially in those that have been exposed the most. In addition, simple measures like pica management can be effective,[90] especially since routine screening for blood lead levels in all children admitted to a psychiatric inpatient unit appears to be neither efficacious nor cost effective.[91]

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Δεν υπάρχει όριο ασφαλείας για την έκθεση στον μόλυβδο: Μια βιβλιογραφική ανασκόπηση

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Ο μόλυβδος αποτέλεσε έναν από τους πιο επικίνδυνους τοξικούς περιβαλλοντικούς παράγοντες στον δυτικό κόσμο, και εξακολουθεί να αποτελεί κίνδυνο σε πολλές περιοχές του πλανήτη. Η νευροτοξική του δράση είναι πολύ έντονη και σε μεγάλο βαθμό τα όρια ασφαλείας της συγκέντρωσής του στο αίμα παραμένουν άγνωστα. Σκοπός της παρούσας εργασίας είναι η βιβλιογραφική ανασκόπηση του θέματος από τη μεριά της κοινωνικής ψυχιατρικής. Δομημένη –με τη χρήση του περιβάλλοντος Dialog Datastar– βιβλιογραφική ανασκόπηση στις βάσεις δεδομένων MEDLINE, EMBASE, CAB Global Health, Cochrane Library γύρω από τις νευροψυχιατρικές εκδηλώσεις της άμεσης και μακροχρόνιας έκθεσης του οργανισμού στον μόλυβδο. Ο μόλυβδος επιδρά στο χολινεργικό, ντοπαμινεργικό και γλουταμινεργικό σύστημα, επεμβαίνοντας με αυτόν τον τρόπο στη φυσιολογική λειτουργία των νευροδιαβιβαστών. Οι νευροτοξικές επιδράσεις του μολύβδου στο κεντρικό νευρικό σύστημα περιλαμβάνουν απόπτωση και τοξικότητα από υπερδιέγερση (excitotoxicity), επιδρώντας στην αποθήκευση και απελευθέρωση νευροδιαβιβαστών και μεταβάλλοντας τους υποδοχείς τους. Τόσο η άμεση όσο και η μακροχρόνια έκθεση στον μόλυβδο προκαλεί σοβαρά νευρολογικά συμπτώματα και πιθανώς μόνιμα γνωσιακά ελλείμματα. Η πιο σοβαρή επίπτωση της δηλητηρίασης από μόλυβδο στα παιδιά είναι η οξεία εγκεφαλοπάθεια, σε συγκεντρώσεις πλάσματος >100 μg/dL στους ενήλικες και 80–100 μg/dL στα παιδιά. Πρώιμα συμπτώματα νευροτοξικότητας από μόλυβδο περιλαμβάνουν ευερεθιστότητα, κεφαλαλγία, διαταραχές προσοχής, τόσο στους ενήλικες όσο και στα παιδιά. Όσο η έκθεση στα παιδιά αυξάνεται, παρουσιάζονται νευροσυμπεριφορικές διαταραχές, όπως μείωση της προσοχής, αδυναμία να ακολουθήσει οδηγίες και εντολές, μειωμένη ενασχόληση με παιχνίδια, χαμηλός δείκτης νοημοσύνης σε επίπεδα πλάσματος 10–35 μg/dL. Μερικές έρευνες υποστηρίζουν πως η γνωσιακή έκπτωση και η μείωση του δείκτη IQ στα παιδιά μπορεί να προκληθεί και σε χαμηλότερες συγκεντρώσεις μολύβδου στο πλάσμα, ακόμη και <10 μg/dL. Το πιο κοινό νευρολογικό σύμπτωμα στους ενήλικες αποτελεί η περιφερική νευροπάθεια, με πτώση καρπού ή/και άκρου ποδός. Μελέτες έδειξαν συσχέτιση μεταξύ προγεννητικής έκθεσης στον μόλυβδο με αντικοινωνική συμπεριφορά και σχιζοφρένεια. Η μακρά έκθεση στον μόλυβδο που καταλήγει σε χαμηλή με μεσαίου μεγέθους συγκέντρωση μολύβδου στο πλάσμα έχει συσχετισθεί με κατάθλιψη, γενικευμένη αγχώδη διαταραχή και άλλες συμπεριφορικές διαταραχές. Υψηλές συγκεντρώσεις μολύβδου στο πλάσμα έχουν συσχετισθεί με ψυχωσικά συμπτώματα, όπως ψευδαισθήσεις και παραληρητικές ιδέες, και πιο σπάνια με ψυχωσικά σύνδρομα. Παρά την απαγόρευση της χρήσης του μολύβδου στη βενζίνη, στα χρώματα και στις σωληνώσεις του νερού, σημαντικές ποσότητες μολύβδου παραμένουν σε υποβαθμισμένες περιοχές σύγχρονων μητροπόλεων, κυρίως στις ζώνες μετάβασης, στα κέντρα των πόλεων, καθώς και σε περιοχές εξόρυξης μολύβδου και στις αναπτυσσόμενες χώρες, ενώ οι ασφαλείς συγκεντρώσεις στο περιβάλλον δεν είναι ακόμα σαφώς καθορισμένες. Ο μόλυβδος αποτελούσε αλλά και εξακολουθεί να αποτελεί έναν περιβαλλοντικό παράγοντα που αυξάνει τη νευ-

ρολογική και ψυχιατρική νοσηρότητα. Επίσης συμβάλλει ιδιαίτερα στην πρόκληση αναπτυξιακών διαταραχών κυρίως σε υποβαθμισμένες περιοχές. Η πρόληψη θα πρέπει να αποτελεί το σημαντικότερο μέσον αντιμετώπισης της δηλητηρίασης από μόλυβδο.

Λέξεις ευρετηρίου: Μόλυβδος, έκθεση, νευροτοξικότητα, όριο ασφαλείας.

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Special article
Ειδικό άρθρο

Dreams in ancient Greek Medicine

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Dreams preoccupied the Greek and Roman world in antiquity, therefore they had a prominent role in social, philosophical, religious, historical and political life of those times. They were considered as omens and prophetic signs of future events in private and public life, and that was particularly accentuated when elements of actions which took place in the plot of dreams were associated directly or indirectly with real events. This is why it was important to use them in divination, and helped the growth of superstition and folklore believes. Medicine as a science and an anthropocentric art, could not ignore the importance of dreams, having in mind their popularity in antiquity. In ancient Greek medicine dreams can be divided into two basic categories. In the first one –which is related to religious medicine– dreams experienced by religionists are classified, when resorted to great religious sanctuaries such as those of Asclepius (Asclepieia) and Amphiaraos (Amfiaraeia). These dreams were the essential element for healing in this form of religious medicine, because after pilgrims underwent purifications they went to sleep in a special dwelling of the sanctuaries called "enkoimeterion" (Greek: the place to sleep) so that the healing god would come to their dreams either to cure them or to suggest treatment. In ancient Greek literature there are many reports of these experiences, but if there may be phenomena of self-suggestion, or they could be characterized as propaganda messages from the priesthood of each sanctuary for advertising purposes. The other category concerns the references about dreams found in ancient Greek medical literature, where one can find the attempts of ancient Greek physicians to interpret these dreams in a rational way as sings either of a corporal disease or of psychological distress. This second category will be the object of our study. Despite the different ways followed by each ancient Greek physician in order to explain dreams, their common intention was to give a rational answer for the creation and content of dreams setting aside any supernatural beliefs. In addition they tried to explain in a scientific way the correlation that could have emerged between the story that took place in dreams and the events that happened in everyday life. Nevertheless, ancient Greek physicians focused especially on nightmares, which were associated with physical problems. For those physicians these nightmares included information about the corporal disease of the patient, which had a reflection in the dream, and they could help them to diagnose the problem in order to restore balance of the body.

Key words: Dreams, antiquity, Greek Medicine.

Introduction

Dreams preoccupied the Greek and Roman world in antiquity; therefore they had a prominent role in social, philosophical, religious, historical and political life of those times.[1–7] Ancient Greek physicians tried to give a rational answer for the creation and content of dreams setting aside any supernatural beliefs.

Regarding the dreams of patients suffering from mental illnesses, ancient Greek physicians believed that their weird dreams and nightmares were a result of the impaired function of their logic, therefore they considered them as a symptom of their disease and were not interested to their thorough examination.

In Corpus Hippocraticum, mania's and dementia's terrible dreams and nightmares are considered as symptom of these diseases and an outcome of brain dyscrasia –bad mixture of brain humors– (Hippocrates Med. et Corp. De morbo sacro 14.1–20,[8] Hippocrates Med. et Corp. De morbo sacro 15.1–22, Hippocrates Med. et Corp. Epistulae 19.1–29,[9] Hippocrates Med. et Corp. De affectionibus interioribus 48.14–29[10]). In this Corpus it is also stated that patients suffering from phrenitis have very figurative dreams (Hippocrates Med. et Corp. Prorrheticon 1.43.1–2),[11] although there is not a direct connection between these dreams and the fever which is a dominant symptom of the disease. Nevertheless, this connection can be found in Corpus Aristotelicum (Aristoteles Phil. et Co. De insomniis 461a.21–3).[12] On the other hand, the mental illness in which patients experience the most turbulent dreams was considered to be melancholy, as it was stated in the most famous ancient book on melancholy written by Rufus of Ephesus (this book is lost but many parts of it were saved by medieval Arab physicians).[13] This conception is also found in Corpus Aristotelicum, where it is emphasized that the most vivid dreams are experienced by patients with high fever, melancholics and drunks. It is also stressed that melancholics have dreams which are distinct (greek: ευθυονειρία) and cause them to wake up violently (Aristoteles Phil. et Co. De divinatione per somnum 464a.24–464b.7.[14] Aristoteles Phil. et Co. De divinatione per somnum 464a.28-464b.3. Aristoteles Phil. et Co. Ethica Eudemia 1248a.29–1248b.7[15]).

Dreams in Corpus Hippocraticum

The earliest medical study on dreams is found in Corpus Hippocraticum and in the book De diaeta (Hippocrates Med. et Corp. De diaeta i-iv 86.1–93.30).[16] The author of this work attempts to present in a scientific way the creation and function of dreams separating them from the art of prediction (Hippocrates Med. et Corp. De diaeta i–iv 87.1–12). In the introduction it is stated that dreams are creations of the soul's vigilance during sleep, because in contrast to relaxed body, soul is on alert making images of body's activities (Hippocrates Med. et Corp. De diaeta i–iv 86.1–14).

The central idea is that dreams reveal the state of human body and are influenced in their development by it. The core of the research lies on the diet.[17] It is believed that diet, in terms of quantity and composition, plays a significant role in the content of dreams, since it is essential for the presence of wetness, dryness and heat in the body which in turn will nominate or disturb the balance of its humors. Dreams therefore reflect the equilibrium (health) or disturbance (disease) of the body. Therefore, if diet reinforces the equilibrium of humors, man will have calm and sweet dreams, but if it provokes disturbance of humors man will have turbulent sleep and nightmares (Hippocrates Med. et Corp. De diaeta i–iv 93.1–30).

The author distinguishes three main thematic categories of dreams. Firstly, the examples of celestial objects are used. Thus, when someone sees the sun, the moon, the sky and the stars clearly this is an indication of good health which should be maintained, sustaining the nutritional choices of the respective days of these dreams. On the event of the opposite the dream reveals some kind of illness either stronger than the strong ones or milder than the mild ones. If a man thinks that the stars are off or harmed or lost or they do not orbit, then if this happens due to air or nebula, these are sings of a mild disease, but if it is due to water or hail there it is sing of serious disease. According to the author all that happen because excreted humor of phlegma has accumulated (Hippocrates Med. et Corp. De diaeta i–iv 89.1–16).

Subsequently, examples about the earth and the natural environment are mentioned. When someone

dreams that he can clearly see or hear the earth, that the earth is smooth and well treated, that the trees are bloomed and fruitful and that the water is clean and calmly runs into the rivers, the sea and the fountains, the man is healthy. When he dreams the opposite there is some kind of disorder. Because if he thinks that he cannot hear or see well, then this is an indication of an illness of the head (Hippocrates Med. et Corp. De diaeta i–iv 90.9–11).

The third section of this work deals with the dead. If someone dreams of the dead being clean, in white clothes and takes something from them which is clean and good, this is an indication of good health. On the other hand, if someone dreams of them being naked, bruised, dirty or them taking or bringing something home, this is a sing of a disease (Hippocrates Med. et Corp. De diaeta i–iv 92.1–10).

Two other passages of this work are of particular interest. The first one refers to a dream, wherein the human traverses rivers and confronts warriors, enemies and bizarre monsters. The author considers it as an indication of a certain disease or mania, thus making the first mention of the possibility of a specific mental disease manifestated in a dream (Hippocrates Med. et Corp. De diaeta i–iv 93.23–25). The second passage is related to the previous one, because again there is a reference to a mental disturbance which affects the content of the dream, but in this case this is probably not a mental illness. More specifically, dreams that have as subject the pointless wandering in various places, declare some agitation of the soul due to an everyday life problem. In fact the solution proposed is to cheer up and try to entertain himself, otherwise there is a risk that these dreams will come true, in two to three days, and become a disease (Hippocrates Med. et Corp. De diaeta i–iv 89.52–57).

Although it would be easy to observe that the author is in the mood of creating a dream-book, similar to those that already appeared in ancient times, in our belief this analogy is only superficial, resulting from the structure of this work, because there is a fundamental difference between this work and other dream-books of antiquity. The author's intention was to create a dreams' list matching each one with the pathological or natural condition that provoked them, in order this study to become a rationalistic medical teaching manual for use by the physicians.

Oberhelman[7] and Jouanna[18] perceived this book as a philosophical rather than a medical one, emphasizing that it reflects the philosophical theories of the macrocosm into the microcosm of the human body and soul. According to our point of view the author's intention was to create a practical medical book concerning the dreams and their rational interpretation, in order to facilitate the exercise of the medical profession in everyday life during the antiquity, having in mind the detailed list of the dreams and their connection to mental or corporal diseases. Therefore, these philosophical ideas were embodied into the text under the theory of humors which derived from the works of Pre-Socratic philosophers,[19] but was converted into a useful and practical medical tool.

Herophilus on Dreams

Herophilus' (ca.320 – 250 BC) views on dreams are saved in short reports by other writers,[20] but they are of particular value. Herophilus has concentrated his interest almost exclusively on intellectual-mental processes about soul functions and its comprehension of the world, but mainly he focused on men's desires, considering them crucial to the creation of dreams. His views are quite different from those of other physicians of antiquity.

Herophilus thought that dreams are divided into three main categories. In the first one he places dreams derived from god, which he considered necessary and inevitable, as Von Staden observed.[20] The only comment we could make for this short report is that this approach is at odds with the rational character of ancient Greek medicine, while the other two categories of dreams according to Herophilus are characterized by their rational context. Into the second category he places natural dreams in which the soul creates images of what is in its best interests. In the third category he lists mixed dreams –as he names them– which occur suddenly, and their context is the idols of man's desires, presenting the example of the lovers who dream of those who love (Pseudo-Galenus Med. De historia philosophica 106.4–8.[21] Pseudo-Plutarchus Placita philosophorum 904.F.6–11[22]).

Setting aside the first category, we will underline that the other two categories define dreams as creations of human desires, which is clearly seen in the

third category and indirectly observed in the second one, because what is in the interest of the soul apparently is associated with desires and expectations. It should be noted that the reference to the term 'idols' should not be limited only to images and scenes of everyday life, but it also incorporates an imprint of emotions and abstract concepts.

Von Staden emphasized that the tripartite distinction of dreams by Herophilus considerably affected the Stoics, and especially Poseidonius, in order to create a similar dream classification scheme. In addition, Von Staden pointed that Herophilus distanced himself from the recognition of disorders or predictions in the dreams.[20] According to our point of view, Herophilus' doctrines on dreams are of particular interest, because they demonstrate an unprecedented, for the antiquity, quest of mental function, distinguishing its autotelic function and approaching several modern theories of the subconscious. Herophilus pointed that man creates the world of his dreams because their context is inspired by man's desires and by his experiences of everyday life which had influenced him.

This thought of him predominates the ancient Greek medicine, regarding the perceptions of the soul. It is obvious that Herophilus limited his concepts solely to the mental sphere, without involving specific views about dreams theory, such as that of the humoral theory, or determining the function of the soul in relation to that of the body, introducing now especially for the dreams the idea of the imaginary, which is decisively determined by the interaction of man with his natural and social environment.

This notion is not exactly in line with the basic principles of ancient Greek medicine, as it considers the soul having a special link to imaginary situations, allowing us to parallel this approach to that of Aretaeus of Cappadocia (2nd or 3rd to 4th c. AD) regarding melancholy, who expressed the idea that sometimes this disease occurs without a disorder of the humors of the body, but due to a disturbance of the soul itself (Aretaeus Med. De causis et signis acutorum morborum 1.5.2.1–1.5.2.4).[23] Both physicians suspected that the mental illnesses and dreams could be solely responsible for the function of the soul. This thesis was difficult to be accepted in ancient times, when the basic principles for the diseases and the function of the soul, physiological or pathological, had a different starting point, mainly the humoral theory. Instead, the emphasis on the soul and the imagery was more suited to philosophical queries, so perhaps this was the reason why Herophilus' theory about dreams was accepted by and further influenced his subsequent philosophical circles that were mentioned above.

According to our point of view, Herophilus highlighted his medical status, and his research on dreams showed that he overcame the stage of "medical dreams", as seen in other ancient physicians. In contrast, we will consider possible that by performing an in-depth study of the imaginary, which he analyzed rationally and by medical standards, he faced the inability to adequately and fully explain according to the rules of ancient Greek medicine –which combined body and soul– the imaginary situations of dreams. That is why he rather opted exclusively for the function of the soul, focusing on human desires, which made him a pioneer of his time.

Rufus of Ephesus on Dreams

Rufus of Ephesus (1st–2nd c. AD) relies on the theory of humors and states his strong belief that corporal humors cause dreams, both good and bad.[24] In fact he states that he has no knowledge of another theory for their interpretation. His views will converge, at least with regard to their general principles, to those encountered in Corpus Hippocraticum (Rufus Med. Quaestiones medicinales 33.1–3).[24]

Rufus of Ephesus deals exclusively with the medical dimension of dreams, perhaps more than any other ancient Greek physician, as he advises that dreams, as well as the general state of sleep, are an important tool for the proper and successful diagnosis. This is why he also underlines that physicians need to ask if the patient slept or not, and if he falls asleep easily or has insomnia, and if there are fantasies or dreams, since all of the above would aid the physician to came to a diagnosis (Rufus Med. Quaestiones medicinales 28.1–29.3).

Rufus of Ephesus states that Myron, a wrestler from Ephesus, while he seemed healthy, he had the following dream. He dreamed that the whole night was in a lake with black, drinking water. When he woke

up, he reported it to his trainer. He did not consider the dream important and permitted him to wrestle. After a while he died. The physician points out that the wrestler would not have died if the trainer had been wise and had made a phlebotomy to Myron before the wrestle (Rufus Med. Quaestiones medicinales 29.4–30.2).

Rufus of Ephesus also mentioned that another person suffering from high fever dreamed many times that he was fighting with an Ethiopian man, who hanged him. The patient reported the dream to a physician, but he did not remember it, before a heavy bleeding from the nose occurred and revealed the disease (Rufus Med. Quaestiones medicinales 31.1–4).

The last incident that is reported by Rufus of Ephesus is the case of a patient who dreamed that he swam in the river Kaystros and died of dropsy (Rufus Med. Quaestiones medicinales 32.1–2).

Comparing the "medical dreams" examined by Rufus of Ephesus to those of Corpus Hippocraticum we realize that their main difference is that they are specific, they describe facts and they are related to the progression of the health of the man who dreamed of them. Nevertheless, their essential similarity is that they signify a physical disorder which caused the situation experienced in the dream. Although they do not constitute a general guide but only a limited group of cases, their aim is to draw the attention of the ancient physician to their crucial diagnostic role.

Galen on Dreams

Galen (129 – ca. 210 AD) has embraced the importance of dreams for medicine, devoting a special work on them, where he analyzed the diagnosis through dreams. Complying with the lessons of the earlier physicians and honoring the findings of the ancient Greek medicine, he also considers dreams as reflections of the physical condition of the patient.

Galen recognizes the disequilibrium of humors as the main cause of dreams, so that the form of the dream is associated with the characteristics and qualities of the humor, and in this way he goes along with the thoughts developed in the corresponding work of Corpus Hippocraticum. This agreement of opinions will be even more obvious when nutrition and weather will be taken into account as shapers of dreams.

Galen also adds the psychological factor, which is determined by the events of everyday life and by the human wishes which disrupt mood, pointing a diversity from Corpus Hippocraticum, because there the revival of everyday incidents is a health component while in this work they are highlighted for their negative impact.

Galen starts this work with the assumption that the dream testifies the mood of the body, so that he matches the types of humors with the dreaming representations, citing general examples. That is, dreaming of fire may be caused by yellow bile and dreaming of smoke or fog or of deep darkness could be due to black bile, as well as dreaming of rain and chill may testify a wetness excess. Additionally, dreaming of snow, ice and hail imply the existence of cold phlegm. He believes that it is important to monitor the weather and the received food. According to him whoever dreams of snowing is considered to suffer from paroxysmic shivering, therefore the attention must be drawn to the body (Galenus Med. De dignotione ex insomniis 6.832.1–6.833.7).[25]

Subsequently, the author analyzed the impact of daily events. It is mainly pathologic conditions in the body that occur during sleep, resulting in the patient experiencing the dream and being able to realize it when he wakes up. Therefore, divination plays only a secondary role (Galenus Med. De dignotione ex insomniis 6.833.7–18).

He argues in favor of this analysis using the following cases. One man dreamed that his leg turned into stone and people judged that this was about the suffering of the slaves, but his leg paralyzed and no one could have foreseen it. A wrestler dreamed that he was in a tank of blood and when he was waked up he was found full of blood and had to be cleaned. He also referred that some people sweat and deciding to take a bath they imagine that they swim in tanks of warm water. Also, the fantasy of drinking without relieving ones thirst is quite often, as well as that of eating or having sexual activity, for those who lack these activities. It seems that during sleep the soul dives in the depths of the body, separates from the sensible and feels the mood and the desires of the body, transforming them into reality through the

dreams. We notice that these views are compatible especially with those of Herophilus about the connection of dreams with desires (Galenus Med. De dignotione ex insomniis 6.833.18–6.834.16). Galen concludes that the desires or the plots of the dreams testify a lot about the absence, redundancy and quality of humors in the human body, accepting the Hippocratic views on the issue (Galenus Med. De dignotione ex insomniis 6.834.16–6.835.14).

Conclusion

After examining the views on dreams of many of the most important ancient Greek physicians the main conclusion to be drawn is that these physicians denied the divine nature of dreams, and the majority of them considered the plot of the dreams as sings of the medical condition of the body which was determined by the status of the corporal humors. According to them the dyscrasia of humors leads to nightmares, while the eycrasia of humors leads to calm and cheerful dreams. Their belief that the dreams were signs of physical disorders resulted in their effort to determine the 'medical dreams', as we can name them, that is their effort to correlate specific dreams to specific conditions of the body. Their empirical observations allowed them to correlate human desires and the function of the soul in the formation of dreams. But due to the fact that ancient Greek medicine was unable to understand the independent role of mental function and of psychology, as we understand it today, the importance of desires was considered secondary. The only real exception was Herophilus, but despite his effort to highlight the role of desires in dreams, this could not be distant from humor's theory.

Τα όνειρα στην αρχαία Ελληνική Ιατρική

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Τα όνειρα (ενύπνια) απασχόλησαν ιδιαίτερα τον κόσμο στην ελληνική και ρωμαϊκή αρχαιότητα, γι' αυτό και κατείχαν εξέχουσα θέση στην κοινωνική, φιλοσοφική, θρησκευτική, λατρευτική, ιστορική και πολιτική ζωή εκείνων των χρόνων. Ως κύριος ρόλος τους αναγνωρίστηκε το γεγονός: θεωρούνταν οιωνοί και προφητικά σημεία για τα μελλοντικά γεγονότα της ιδιωτικής και της δημόσιας ζωής, πράγμα που τονίζονταν ιδιαίτερα όταν στοιχεία των διαδραματιζομένων κατά τη διάρκεια των ονείρων συσχετίζονταν άμεσα ή έμμεσα με τα εξελισσόμενα μελλοντικά γεγονότα. Γι' αυτό άλλωστε θεωρούνταν σπουδαία η χρήση τους στη μαντική τέχνη, ενώ έδιναν τροφή για την ανάπτυξη των προλήψεων, της δεισιδαιμονίας και των λαϊκών δοξασιών. Η ιατρική ως επιστήμη και τέχνη που έχει ως επίκεντρο τον άνθρωπο, ήταν αδύνατο να αδιαφορήσει ή να μείνει ανεπηρέαστη από τα όνειρα, ειδικά μάλιστα κατά τους αρχαίους χρόνους, οπότε και είχε ιδιαίτερη διάδοση η ενασχόληση με αυτά. Στην αρχαία ιατρική τα όνειρα μπορούν να διακριθούν σε δύο βασικές κατηγορίες. Η πρώτη αφορά τη θρησκευτική ιατρική όπου κατατάσσονται τα όνειρα που βίωναν οι πιστοί όταν κατέφευγαν στα μεγάλα θρησκευτικά-ιαματικά κέντρα, δηλαδή στα ιερά του Ασκληπιού (Ασκληπιεία) και του Αμφιάραου (Αμφιαράεια). Οι πιστοί έφταναν σε αυτά τα ιερά, υποβάλλονταν σε καθαρμούς και υφίσταντο την «εγκοίμηση», δηλαδή κοιμούνταν σε ειδικό χώρο, το εγκοιμητήριο, με σκοπό να έρθουν στον ύπνο τους σε επικοινωνία με τη

θεότητα, τον Ασκληπιό ή τον Αμφιάραο, η οποία και θα τους πρόσφερε την ίαση ή θα τους υποδείκνυε τη θεραπεία. Υπάρχουν πολλές αναφορές για τις εμπειρίες που βίωναν οι πιστοί κατά την εγκοίμηση, οι οποίες όμως αν δεν πρόκειται για φαινόμενα αυθυποβολής, χαρακτηρίζονται ως προπαγανδιστικά στοιχεία από το ιερατείο κάθε ιερού, με στόχο τη διαφήμισή του. Στη δεύτερη κατηγορία κατατάσσονται οι ειδικές αναφορές των αρχαίων Ελλήνων ιατρών στα συγγράμματά τους σχετικά με τα όνειρα, όπου γίνεται προσπάθεια ερμηνευτικής προσέγγισής τους, η οποία όμως βασίζεται στους κανόνες της επιστήμης, όπως αυτή είχε διαμορφωθεί στους αρχαίους χρόνους. Μερικοί από τους σπουδαιότερους ιατρούς της αρχαιότητας αφιέρωσαν διάφορα κεφάλαια στο θέμα. Παρά τον διαφορετικό τρόπο που προσεγγίζει ο καθένας από αυτούς το συγκεκριμένο φαινόμενο, θα μπορούσαμε να εξαγάγουμε ως διαπίστωση κοινή για όλους, ότι πρόθεση και μέλημά τους ήταν να δώσουν μια ορθολογική απάντηση για τη δημιουργία και το περιεχόμενο των ονείρων, παραμερίζοντας οποιεσδήποτε δοξασίες μπορούσαν να προκύψουν. Ακόμη προσπάθησαν να ερμηνεύσουν με τον τρέχοντα επιστημονικό τρόπο τον συσχετισμό που θα μπορούσε να αναδειχτεί μεταξύ της ιστορίας που διαδραματίζονταν στα όνειρα και στα γεγονότα που συνέβαιναν στην καθημερινή ζωή. Επειδή ο ορθολογισμός ήταν το απόλυτο κριτήριο των ερμηνειών τους, για τον λόγο αυτό παρατηρούμε ότι οι αρχαίοι Έλληνες ιατροί επικεντρώνονταν σε όνειρα και κυρίως στους εφιάλτες, τα οποία συσχετίζονταν κυρίως με σωματικά προβλήματα των ανθρώπων. Δηλαδή, γι' αυτούς είναι στοιχεία νόσου και μαρτυρούν ότι υπάρχει κάτι παθολογικό στον ανθρώπινο οργανισμό, το οποίο έχει την αντανάκλασή του μέσα στο όνειρο. Θεωρούνται δηλαδή συμπτώματα μιας εκτροπής του οργανισμού που πρέπει εκείνοι να τη διαγνώσουν, ώστε να αποκαταστήσουν την ισορροπία στον ανθρώπινο οργανισμό.

Λέξεις ευρετηρίου: Όνειρα, αρχαιότητα, Ελληνική Ιατρική.

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Case report
Ενδιαφέρουσα περίπτωση

Restless legs syndrome mimicking S1 radiculopathy

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A case of a chronic idiopathic form of a severe type of Restless Legs Syndrome (RLS), which developed during pregnancy and persisted after this, misdiagnosed for 34 years as radiculopathy S1, is reported. In spite of the thorough clinical and laboratory investigation, in addition to constant changes of the therapeutic approach, the diagnosis of S1 radiculopathy could not be confirmed, resulting in a chronic clinical course; the latter was characterized by relapses and remissions not attributed or linked in any way to the treatment (various types of). In fact, it was due to a routine workup in a sleep clinic, where the patient was referred because of a coincident chronic insomnia (Restless Legs Syndrome is a known and important cause of insomnia/chronic insomnia), which resulted in a proper diagnosis and treatment of this case. With the use of Restless Legs Syndrome appropriate treatment (Pramipexole 0.18 mg taken at bedtime, a dopaminergic agent and Level A recommended drug for Restless Legs Syndrome) an excellent response and immediate elimination of symptoms was achieved. Restless Legs Syndrome may present with a variety of symptoms (with the most prominent shortly being reported with the acronym URGE: Urge to move the legs usually associated with unpleasant leg sensations, Rest induces symptoms, Getting active brings relief, Evening and night deteriorate symptoms); given the fact that Restless Legs Syndrome presents with a great variety and heterogeneity of symptoms (mostly pain, dysesthesia and paresthesia), which may occur in several other diseases (the so called "RLS mimics"), proper diagnosis of Restless Legs Syndrome usually fails. Restless Legs Syndrome misinterpreted as S1 radiculopathy, to the best of our knowledge, has not been reported yet in the literature. Here, case history, clinical course and common RLS mimics are presented. Different forms of Restless Legs Syndrome manifestations, which are commonly –as in this case– misinterpreted due to their mimicking several pathological conditions, Restless Legs Syndrome prevalence on general population according to various large epidemiological studies and pathogenic hypotheses on the issue of Restless Legs Syndrome are discussed. Finally, by presenting another possible "RLS-mimic" our aim is to highlight the common misdiagnosis of Restless Legs Syndrome, which can mimic a variety of disorders, some of which are very common, such as an S1 radiculopathy, thus raising concern among doctors of various specialties addressed to by Restless Legs Syndrome sufferers, on the importance of proper diagnosis of the syndrome.

Key words: Restless legs syndrome, misdiagnosis, S1 radiculopathy.

Introduction

Restless legs syndrome (RLS) is a common disorder and its prevalence has been underestimated in the past; population-based studies estimate it to be between 3–10%.[1–3] RLS, which is either idiopathic or secondary to renal failure, pregnancy or iron deficiency and is more frequent in women,[1,2] according to the current diagnostic criteria, is defined by four key features,[2] shortly reported also with the acronym URGE;[4,5] U: urge to move the legs usually associated with unpleasant leg sensations, R: rest induces symptoms, G: getting active brings relief, E: evening and night deteriorate symptoms. RLS is often under-diagnosed due to misdiagnosis of several other pathologic conditions, such as musculoskeletal/connective tissue diseases, movement disorders, peripheral vascular disease, depression, respiratory disorders, etc.[1,3] Here, we present a woman suffering from RLS (chronic form), misdiagnosed as S1 radiculopathy for 34 years.

Case history

A 56 year old Caucasian female, at the age of 22 during her first pregnancy, first complained of numbness, tingling and dull pain localized to the lower back, at the lumbar-sacral junction, bilaterally; these symptoms were projecting from the posterior thigh and leg to the soles of the feet, bilaterally. The symptoms together with an irresistible urge to move the legs used to occur at rest and mostly in the evening and/or at bedtime; thus, prolonged immobilization as when travelling or watching a movie was intolerable, and symptoms were relieved only by moving/stretching her legs and her back and/or by walking. Her sleep was also severely affected due to difficulty falling asleep. After delivery, there was a brief period of remission, but soon the symptoms reappeared. At that time her primary care physician, during a routine clinical examination, suspected an S1 radiculopathy and prescribed non-steroidal anti-inflammatory (NSAID) together with muscle relaxant drugs; there was no improvement. Following that, and in the next years, the patient performed repeated clinical (mainly orthopedic) and non-clinical investigations: imaging (CT/MRI) (figure 1), blood tests (standard including also ferrum/ferritin, thyroid function, Vit. B_{12}/folic acid, and standard rheumatic assessment), which were all normal. Despite the absence of clear clinical and/or non-clinical evidence, and based mostly on the symptoms referred by the patient, chronic relapsing-remitting S1 radiculopathy diagnosis was made and the patient underwent several therapeutic approaches comprising NSAID, steroidal drugs, tricyclic antidepressants and physiotherapy, without any benefit. Brief periods of remission (maximum of a few months), were not related to therapies.

We saw the patient at the age of 56 (in 2012) due to her chronic symptomatology, which has been in-

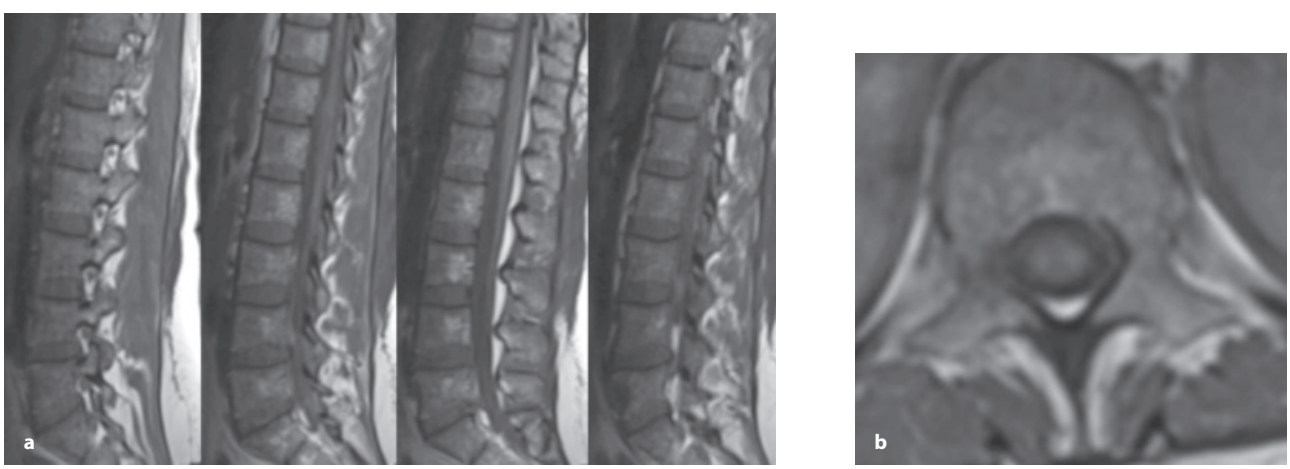

Figure 1. (a) Sequence of 4 normal sagittal sections of the lumbar-sacral part, (b) Normal S1 transverse section.

variant since the age of 22 and was burdening her activities of daily living, primarily her social life and her sleep. Neurological examination was normal; no sensory symptoms or deficits were noted, Lasègue sign was negative bilaterally, muscle strength was normal and deep tendon reflexes (both knee and ankle) were brisk bilaterally. An electrophysiological study, including motor conduction velocity of the peroneal and tibial nerve and sensory conduction velocity of the sural nerve bilaterally, was normal. Finally, because of her chronic insomnia (more than an hour needed for falling to sleep), the patient underwent a sleep workup; RLS criteria[4] were met, while with an RLS severity score of 23/40 (severe type). Pramipexole (a dopaminergic agent and Level A recommended drug for RLS5) 0.18 mg at bedtime was started, with an excellent response: all symptoms disappeared since the first night.

Discussion

In our patient, RLS onset occurred during pregnancy, a well-known risk factor for transient RLS,[6] and thereafter –except from a few symptom-free periods of time– she continued to suffer. There is recent evidence which supports the hypothesis that the transient pregnancy RLS form is a significant risk factor for the development of a future chronic idiopathic RLS form.[7] Moreover, the patient complained for chronic insomnia. Insomnia and disturbed sleep are among the most common associated features of RLS.[2] The pathogenesis of the syndrome remains unclear but the excellent response to levodopa and dopaminergic agonists offers a strong evidence for the role of a dopaminergic system in RLS pathogenesis;[1,2] in fact, our patient responded perfectly to the dopaminergic therapy; the immediate response of low-dose dopaminergic therapy is included among the supportive RLS diagnostic criteria.[2]

RLS is a common but still under-diagnosed disorder with a negative impact on quality of life.[1–3] In a large epidemiological multicenter study among primary care centers in USA and four different western countries, which comprised 23.052 patients, primary care physicians correctly recognized this disorder in only 7.7 and 13.6% of cases (mild and severe RLS respectively).[1] Another vast population study among primary care physicians in 6 western European countries comprising 10.564 patients, performed several years after the introduction of the existing RLS diagnostic criteria which have added further specificity and sensitivity to RLS diagnosis and increased the disease-awareness, revealed that despite repeated consultations for over one year regarding several symptoms –including those related to RLS– diagnosis was give only to 9% of the patients.[3] The previously mentioned data are mostly due to the vast symptomatology of RLS (i.e., pain, dysesthesia, paresthesia), which may "mimic" other pathologies, mainly back pain, joints and circulation diseases, myalgia, anxiety/depression, while arthritis and neuropathy are less frequently reported.[1,8] That is why RLS sufferers frequently consult phlebologists/vascular surgeons, rheumatologists and cardiologists, rather than neurologists or sleep experts (mainly in the US).[1] However, no reports of RLS misdiagnosed as S1 radiculopathy exist in the literature, while among the secondary forms of RLS, sporadic cases of RLS following myelopathy, spinal cord lesions or lumbosacral radiculopathy are reported.[9,10] Moreover, proper diagnosis of RLS becomes even more difficult in cases of co-morbid back pain, lumbar disc diseases or radiculopathy:[8] RLS prevalence in the context of lumbar radiculopathy has been reported to be up to 68%.[11] On the other hand "over-diagnosis" of RLS, i.e. in common conditions such as cramps or local leg pathology, which fulfill the RLS diagnostic criteria, may further complicate the RLS diagnostic issue.[12]

In summary, RLS diagnosis is difficult and at times fairly complicated. However, symptomatology compatible with back pain and/or radiculopathy, but with atypical features (i.e., normal neurological examination, circadian distribution of the phenomenology, unresponsiveness to painkillers/physiotherapy, amelioration of the symptoms following movement and co-morbid disturbed sleep – especially insomnia) should include RLS in the differential diagnosis.

Σύνδρομο ανήσυχων άκρων διαγνωσμένο ως ριζοπάθεια Ι1

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Στο παρόν άρθρο (παρουσίαση περιστατικού) γίνεται η περιγραφή μιας περίπτωσης γυναίκας 56 ετών πάσχουσας από σύνδρομο ανήσυχων άκρων (Restless Legs Syndrome, RLS) χρόνιας ιδιοπαθούς μορφής, το οποίο παρουσιάστηκε μετά από την εγκυμοσύνη, ενώ είχε λανθασμένα διαγνωσθεί ως ριζοπάθεια Ι1 για 34 χρόνια. Το σύνδρομο ανήσυχων άκρων είναι μια συχνή νευρολογική κινητική διαταραχή του ύπνου, η οποία χαρακτηρίζεται από μια πλειάδα συμπτωμάτων: κυρίαρχα συμπτώματα αναφέρονται η ανάγκη για κίνηση των άκρων που συχνά συνοδεύεται από δυσάρεστο αίσθημα στα άκρα, η επίταση των συμπτωμάτων με την ξεκούραση, η ανακούφιση με την κινητοποίηση, και η επιδείνωση κατά τις απογευματινές και νυχτερινές ώρες. Όλα τα παραπάνω συμπτώματα, μη όντας ειδικά για τη συγκεκριμένη νόσο και επειδή πολύ συχνά ομοιάζουν με συμπτώματα άλλων κοινών παθήσεων, συχνά στην καθημερινή πράξη αντιμετωπίζονται από διαφορετικές ειδικότητες ιατρών (π.χ. γενικοί ιατροί, παθολόγοι, ορθοπεδικοί, κ.λπ.) ως συμπτώματα άλλων παθήσεων. Αυτός είναι και ο σκοπός του παρόντος άρθρου, δηλαδή η ανάδειξη του γεγονότος ότι η νόσος ανήσυχων άκρων (RLS) –καίτοι ένα σύνδρομο που απαντάται συχνά στον γενικό πληθυσμό (σε ποσοστό 3–10%)– πολύ συχνά είτε υποδιαγιγνώσκεται είτε του αποδίδεται λανθασμένη διάγνωση (όπως εν προκειμένω η ριζοπάθεια). Στη βιβλιογραφία δεν υπάρχουν αναφορές σχετικά με λανθασμένη διάγνωση RLS ως ριζοπάθεια Ι1, ως εκ τούτου το παρόν είναι το πρώτο περιστατικό. Παρουσιάζεται το περιστατικό με λεπτομερή αναφορά στο ιστορικό, στην κλινική εικόνα, στη διαφορική διάγνωση, καθώς και στη θεραπευτική αντιμετώπισή του. Συγκεκριμένα, παρά τον συστηματικό κλινικό και εργαστηριακό έλεγχο στον οποίο υπεβλήθη η ασθενής αλλά και τις συνεχείς αλλαγές της φαρμακευτικής αγωγής, η διάγνωση και αντιμετώπιση ως ριζοπάθεια Ι1 δεν επιβεβαιώθηκε, και η κλινική πορεία του συνδρόμου ανήσυχων άκρων –με εξάρσεις και υφέσεις ανεξάρτητες της όποιας θεραπείας– συνεχίστηκε επί μακρόν. Ένας ενδελεχής και συστηματικός έλεγχος σε ιατρείο ύπνου, στο οποίο η ασθενής παραπέμφθηκε λόγω χρόνιας συνοδού αϋπνίας, έθεσε τη σωστή διάγνωση βαρείας μορφής συνδρόμου ανήσυχων άκρων, καθώς και την ενδεδειγμένη θεραπεία, με την οποία επετεύχθη άριστη ανταπόκριση και πλήρης υποχώρηση των συμπτωμάτων ήδη από την έναρξή της. Συμπερασματικά, διερευνώνται η πολυμορφία στην εμφάνιση των συμπτωμάτων του συνδρόμου (τα οποία συχνά, όπως και στην περίπτωση που παρουσιάζεται στο παρόν άρθρο, μιμούνται άλλες παθήσεις, με αποτέλεσμα τη λανθασμένη διάγνωση και θεραπευτική αντιμετώπιση), η επίπτωση στον γενικό πληθυσμό –όπως προκύπτει από μεγάλες επιδημιολογικές μελέτες–, καθώς και οι αιτιοπαθογενετικές υποθέσεις που έχουν γίνει σχετικά με το εν λόγω σύνδρομο. Επισημαίνεται η ανάγκη ευαισθητοποίησης και εκπαίδευσης των ιατρών διαφόρων ειδικοτήτων, στους οποίους συχνά απευθύνονται οι ασθενείς με RLS, όσον αφορά στην ύπαρξη και τη σωστή διάγνωσή του.

Λέξεις ευρετηρίου: Σύνδρομο ανήσυχων άκρων, λανθασμένη διάγνωση, ριζοπάθεια Ι1.

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