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**University Clinic of Psychiatry
41 Nicolae Romanescu St., 200317 Craiova, ROMANIA
Tel: +40 251 426020; Fax: +40 251 428584
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On the Cover:

ION ȚUCULESCU (1910-1962)

Portretul soției
Portrait of the wife

EDITORIAL

Tudor Udristoiu, Editor-in-Chief

During the last decade, the psychiatric and somatic challenges associated with the alcohol addiction have radically changed concerning the conceptual and therapeutic approach, the updates in the understanding of the biological and psycho-social mechanisms, but also the acceptance of the failure of the „traditional” therapeutic strategies.

The lifetime and 12-months prevalence of the alcohol abuse is 17.8% and 4.7% respectively, while the rates for alcohol dependence are 12.5% and 3.8%; the risk for alcohol dependence and psychiatric and somatic complications is higher for male, younger, unmarried and with lower income adults (1). The treatment gap is estimated around 75% in USA and 90% in Europe (2). As many as 80% of men and 60% of women in developed countries drink at some time during their lives. Moreover, women may be at a higher risk for the fetal alcoholic syndrome. Heavy drinking can cause mild anterograde amnesias, temporary cognitive deficit, sleep problems, peripheral neuropathy, gastrointestinal problems, decreased bone density and reduced production of blood cells and could also generate the fetal alcohol syndrome (3).

The majority, if not all medical conditions, are aggravated or triggered by alcohol abuse or dependence. In the first row stand cerebral, cardio-vascular and hepatic disorders, as well as cancer. On the other hand, moderate alcohol consumption may reduce the risk for cardio-vascular disorders, stroke or metabolic disturbances.

The morbidity and comorbidity through alcohol abuse and dependence covers the entire psychiatric pathology and contribute directly to the antisocial and suicidal behaviors. And let's not forget the frequent association of the alcohol abuse with illicit drugs. Daily clinical experience offers many examples of familial, professional and social impairments caused by alcohol abuse or dependence, with multiple negative consequences and significant direct and particularly indirect expenses of the community.

From a different perspective, there is an important sector, especially in our country, that goes overlooked by research and regulatory factors: the action of other substances, more or less approved, that are added in alcoholic beverages.

Alcohol abuse and dependence is considered a major risk factor in the course of any somatic or psychiatric disorder. Based on the epidemiological facts regarding the alcohol consumption, alcohol dependence and psychiatric and somatic comorbidities, the challenges of the alcohol addiction therapy are a matter of public health. In this frame, the new conceptual paradigm in alcohol-related pathology should determine the change from the moralist model, based on total abstinence, to the achievement of controlled, moderate consumption and prevention of somatic and cerebral

consequences of alcohol abuse. The medical models, introduced by Watts at the beginning of the '80s (4), are gaining support by referring mainly the medical aspects: the evidence-based medical approach and the recognition of the nosological frame of alcohol abuse and dependence, based on genetic, biological, psychological and social facts.

From the biological perspective, the opioid receptors play a significant role in modulating the dopaminergic and serotonergic brain circuits that may be involved in the mechanisms of addiction and action of novel therapies that raise the dopamine levels in the nucleus accumbens. Highlighting these mechanisms may sustain the possibility of a secondary prevention, thus freeing the patients from craving and stigma. The use of the new therapeutic strategies could control the somatic comorbidities, including a lower incidence of the fetal alcoholism syndrome, as well as functional and social alcohol-related disabilities, with significant decrease of the social and economic costs of alcohol abuse and dependence.

From the prevention perspective, identifying specific biomarkers for every pattern of alcohol consumption, ranging from recent heavy drinking to genetic predisposition will allow a better approach in the care of alcohol-related problems. Although research continues to report biomarkers with a higher specificity and sensitivity than the ones usually employed in clinical practice, the development of new classification panels based on these traits is still behind reality (5).

The pharmacological progress will allow in the near future a differentiated therapeutic approach, based on the course stage of alcohol addiction and the structural and functional impairments of the brain, by using predominantly acamprosat in alcohol withdrawal syndrome, naltrexone in controlling the acute psychotic interferences and nalmefene in preventing the relapses and gaining control over the consumption.

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RETT SYNDROME: CLINICAL, ETHIOLOGICAL AND THERAPEUTIC CONSIDERATIONS. A CASE REPORT.

Elisabeta Racos-Szabo¹, Iosif Gabos-Grecu^{1,2}, Cristian Gabos-Grecu¹, Marieta Gabos Grecu^{1,2}, Al Hussein Hussam¹, Elena Gabriela Buicu^{1,3}

¹University of Medicine and Pharmacy, Tirgu Mures, Romania

²Psychiatric Clinic No. 1, Tirgu Mures, Romania

³Mental Health Center, Tirgu Mures, Romania

Abstract

Introduction: RETT syndrome is a neurodegenerative disorder that almost always occurs in girls with an incidence of 1:15000 or 1:20000. The neuropsychometric and somatic development is normal in the first year of life, and subsequently microcephaly and progressive loss of mental acquisition appears and loss of language and of the neuro-motor abilities. Among the early neurological symptoms are included ataxia and tremor of the hands. Specific symptoms of the RETT syndrome include: loss of the use of hands and the occurrence of spontaneous stereotyped movements on the midline namely „hands washing“ hitting or rubbing them. Respiratory disorders with outburst of hyperventilation, apnea and cyanosis are also present.

Material and method: It is to be submitted the case of a 5 year old girl diagnosed with RETT syndrome and supervised at the Tg.-Mures NPP Clinic from the age of three years old. Neurological clinical examination, psychiatric and psychological examination, EEG monitoring, clinical observation were made and eventually it was established the diagnosis of RETT syndrome, stage III.

Discussion: RETT syndrome is caused by MECP2 gene (Methyl-CpG binding protein 2) located on the long arm of chromosome X - q28. In boys were described point mutations of the gene, clinically presenting mental retardation and spastic paraparesis. The diagnosis was established on the basis of indispensable criteria, on the associated clinical symptoms, on exclusion criteria, the disease is a encephalopathy progressive with progression towards degradation, with loss of neuro-motor and mental perceptions, leading to dementia with autistic symptoms. The patient received antiepileptic treatment, neuroborant, kineto-therapy, multisensory stimulation, specific stimulations (ABA).

Conclusions: The case was interpreted as an evolutionary stage III RETT syndrome. The peculiarity of the case is that the patient presented the perinatal distress with circular cord and Apgar score 8, normal head circumference at birth, with initial corresponding development in the neuro-psycho-motor traits until around the age of 2 years.

Key words: RETT syndrome, clinical presentation, autistic behavior.

¹ Correspondence: Iosif Gabos-Grecu, Gh. Marinescu St., no. 38, Tirgu Mures, Romania.
Tel.: +40 744 512724; e-mail: gabos@orizont.net

RETT syndrome was described in 1966 by Andreas Rett, Viennese physician, as a condition of girls which consisted of cerebral atrophy with hyperammonemia. In 1983 the syndrome was recognized by Hagberg and Aicardi by the publication of cases described in Sweden, Portugal and France. (6) The condition occurs with an incidence of 1:10000-1:15000 (10), and by others up to 1:22000 or 1:23000, representing $\frac{1}{4}$ to $\frac{1}{3}$ of the progressive developmental disability to girls. (8) Several cases in boys have been described in the literature, compatibility with life in those cases involving a Klinefelter syndrome or a somatic mosaicism. It is a progressive disorder and the only pervasive developmental disorder with a known genetic cause.

The gene for RETT syndrome was identified in 1999 (1.), being located on the long arm of chromosome X - q28, which is called MECP2 (methyl - CpG binding protein 2). Gene mutations occur in most of de novo cases, on the parental X chromosome in 70-80 % of the patients with RETT syndrome. In 2002 Dotti and collaborators described 6 cases of boys with point mutations in the gene, clinically presenting mental retardation and spastic paraparesis.

Essential criteria for the diagnosis of RETT syndrome are:

- Apparently normal psychomotor development until the age of 6 months;
- The pre-and perinatal periods apparently normal;
- Normal head circumference at birth;
- After 6 months to 4 years slowing the rate of growth of head circumference;
- Between 6 and 30 months loss of voluntary use of hands associated with impaired communication and socialization;
- Absence of language development and severe psychomotor retardation;
- Motor stereotypies on the midline of the body: clap, friction or "Washing hands" that appear after spontaneous loss of their use;
- Trunk ataxia and walking apraxia between 1 and 4 years (7).

In addition to the criteria mentioned above, the following associated clinical symptoms appear in RETT syndrome:

- Electroencephalographic abnormalities: impoverishment of the base rate and occurrence on sleep routes of polytopic head flushes and complex tip-wave, sometimes routes with slowly diffuse disorganization of the route with hypsarrhythmic aspect;
- Epileptic seizures that sometimes precede any other clinical symptoms and may include: infantile spasms, focal or generalized seizures;
- Respiratory disorder: bouts of hyperventilation, sleep apnea, abdominal movements with forcibly expelled air, episodes of stopping breathing (breath holding);
- Spasticity, muscle atrophy, dystonia;
- Scoliosis;

- Vegetative disorders in the extremities;
- Delay in somatic development;
- Leg weakness (8).

The condition is characterized by an initial normal psychomotor and somatic development in the first 6-18 months of life, then stagnation in developing procurement and then produces a rapid deterioration of the psychic state and behavior leading to dementia with autism clinical signs (5).

RETT syndrome evolves in four stages, namely:

- **Stage I:** Early stagnation in development with onset between 6 and 18 months consisting in disinterest in toys and company, delay of the head circumference growth with microcephaly, appearance of hypotonia. This stage can last for months;
- **Stage II:** onset between 1 and 4 years old, consisting of massive and rapid destruction leading to rapid deterioration of the neuropsychiatric behavior, loss of spontaneous movements of hands and ability to use them, seizures, stereotypies of hands, grimacing, mental and visual discontact, loss of expressive language, insomnia, clumsy motility disorders, self-harm behavior (they beat their hands, they slap themselves etc.), EEG abnormalities. This stage can last for weeks or months;
- **Stage III** in image of stabilizing appearance, onsets between 2-10 years and consists of: seizures, specific stereotypies of the hands (washing hands), severe mental retardation, autistic behavior but with some regression of symptoms, ataxia, spasticity, respiratory disorders (hyperventilation, apnea), weight loss, changes in the EEG. This stage can last several months or years;
- **Stage IV** with motility damage after the age of 10-12 years consists of: scoliosis, stiffness, muscle atrophy, pyramidal signs, loss of motility with wheelchair restraint, the absence of receptive and expressive language, severe limb trophic disorders, somatic retardation, lasting for years (6).

The **exclusion criteria** in RETT syndrome are also known, namely: congenital microcephaly, pre- and perinatal distress, hypotrophy at birth as a sign of intrauterine suffering, metabolic abnormalities, neurological organic diseases, erodegenerative disorders, secondary brain lesions after a brain injury or a CNS infection (8).

Life expectancy of patients with RETT syndrome is variable, but there is also the possibility of sudden death (8). In the Nordic countries it was reported the existence of cases of RETT syndrome with survival for decades. There is no etiologic treatment in RETT syndrome. Following investigations by functional imaging it was revealed nonspecific brain atrophy and research in neurobiology to suggest abnormalities of the dopaminergic path and endorphins.

Decrease in the LCR of the levels of metabolites of the dopaminergic and cholinergic system, and increasing the concentration of endorphins also led to attempts to use Naltrexone in the treatment, with inconclusive effects (9).

In RETT syndrome is made symptomatic treatment, namely antiepileptic treatment and neuroborant treatment, complex recovery therapy by kinetotherapy, correction of scoliosis and last but not least specific therapy for the autistic part (11). We remind the ABA technique (Applied Behavior Analysis, PECS (Picture Exchange Communication System) and an adapted educational program.

We present the case of P.D. girl, aged 5, hospitalized for the first time in the Pediatric Clinic of Neurology and Psychiatry Tg-Mures in November 2010, at the age of 3 years, for epileptic seizures consisting in generalized hypotony and generalized tonic contracture with loss of consciousness for 1-2 minutes, mental and visual discontact, motor stereotypies with the hands on median line, rarely playing with the breath, improper use of hands to usual activities. The patient comes from physiological pregnancy, birth at 41-42 weeks, triggered by oxytocic ENP, fetus of 3700 grams with the circular umbilical cord, head circumference of 35 cm, Apgar score 8, severe and prolonged jaundice requiring phototherapy and treatment with Phenobarbital, interpreted as incompatibility O/A group. Neuro-psychomotor development was as the mother stated, initially adequate: sits at 6 months, walks without support at 1.4 years, first words at 1 year old, playing with toys, is attentive, cheerful. From the age of two years the mother observes a mentally regress meaning that she was no more saying the words she said earlier, losses the interest in toys and environment, rarely and weakly makes eye contact with the family members. After the age of two years the first bouts of loss of consciousness appeared, initially in infectious - fever context (3 crisis) with generalized tonic-clonic aspect, and later amyotonic crisis. She is consulted in territorial LSM and is recommended treatment with neuro-roborants: Lucetam, Encephabol syrup, Cerebrolysin. On hospitalization in our Clinic the neurological examination highlights the following: head circumference 45 cm, generalized muscular hypotonia, ataxic walk with wide base and titubations, slight decrease in the segmentation strength of the lower limbs, symmetrical Rot without pyramid reflexes.

Psychological examination reveals the following: superficial and short eye contact, rocking stereotypies and rotation around the body, motor-handed stereotypies: agitation and friction on the midline, leading them to the mouth, vocal stereotypies, bruxism, expressive language with nonsense, soliloquies in jargon, does not touch the objects, breathing game, rarely catches food.

Somatic examination: staturo -weighted hypotrophy, weight: 12,5 kg, paleness of skin, mucous, cold extremities, slightly cyanotic, thin skin vascular network visualization; heart and lung stethacoustic without changes, slender abdomen, no sphincter control.

Paraclinical laboratory tests: Hgl: 11.9 g%, Htc: 36.8%, L: 13000, Tr: 367000, ESR: 9mm / h, SGOT: 59U / L, SGPT: 22U/L, urea: 39.6 mg%, creatinine: 0.59 mg%, Ca: 2.5 mg%, Mg: 1.9 mg%, glycemia: 76 mg%, Bi: 0.2 mg%.

EEG examination at first hospitalization (Fig. 1): theta-delta wide route, with continuous flushing of polymorphic delta waves and slow waves in steep slope with disorganization of the route.

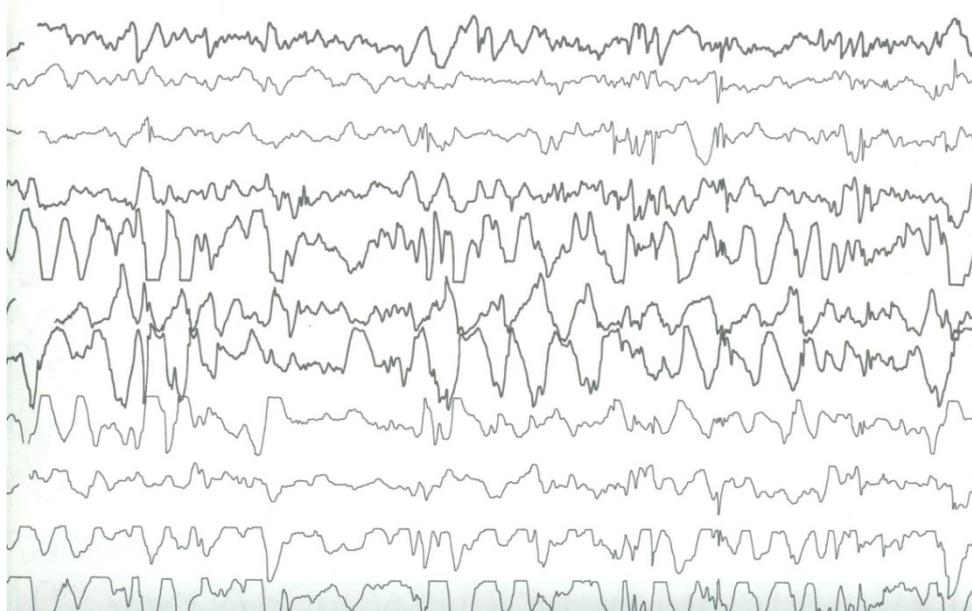


Fig. 1. EEG examination at first hospitalization

Psychological examination: stereotypies with the hands in midline: hands rubbing, repeated touching of the lips, smelling of the objects, does not use the hand with a purpose, absent meaningful expressive language, in observation game breathing, rocking stereotypes, mental and visual discontact. Conclusion: disorder with autism spectrum: RETT syndrome in observation.

FO examination: contoured papillae, normal colored; normal aspect macula.

Rtg. cranium AP and LL: microcephaly skull with open sutures, a few frontal and occipital digital impressions.

Treatment with Depakine syrup, Spironolactone, Tanakan, Vitamin B6, Folic Acid, Encefabol syrup, Cerebrolysin and Vitamin B12, Risperidone 1mg/ml solution was instituted, ABA therapy and multisensory stimulation.

Epileptic seizures have ceased, but is emphasized the breathing game, she shows bouts of hyperventilation, motor stereotypies persist with the hands on the median line, she is sleepy, ataxia gets worse, reason why she is hospitalized again (2011) and she is no longer administered treatment with Risperidone and Depakine but is introduced the treatment with Topiramate. Mother notices a slight psychiatric improvement: she makes superficial eye contact even for longer, occasionally uses the hand to eat pieces of food, and there are no more epileptic seizures.

EEG control examination (Fig. 2): theta-delta route background with repeated flushes, hypervoltated by tip-wave complexes, slow waves in steep slope, and polymorphic delta waves in the right F-C and bilateral T, making irritation lesional focals.

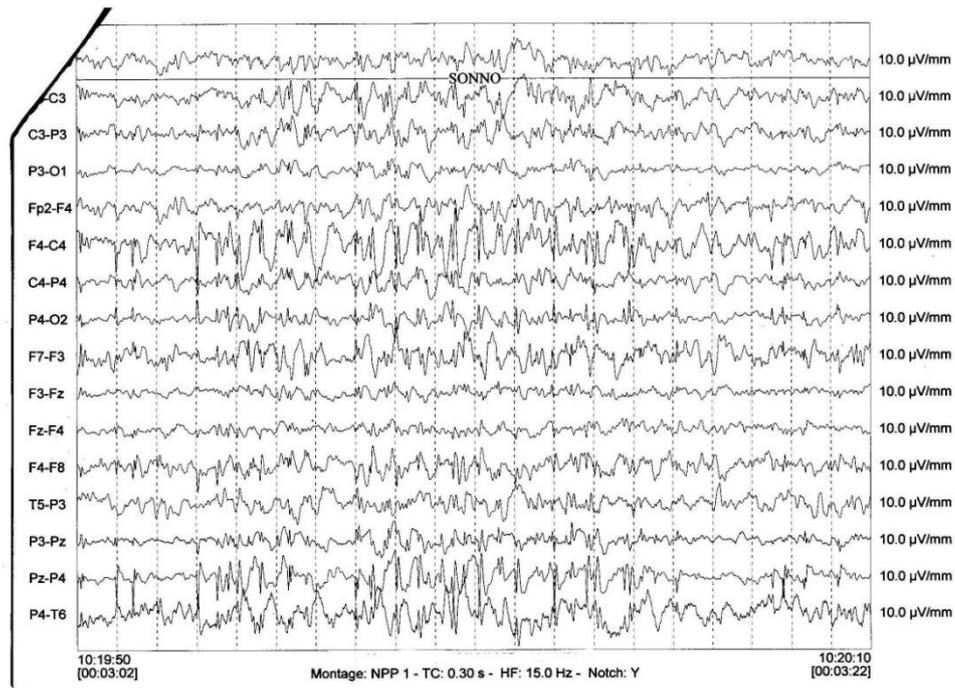


Fig. 2. EEG control examination

Cranial CT (Figure 3, 4, 5): No hetero-dense lesions in the brain substance under or supratentorial and no intracranial fluid accumulation, ventricular symmetrically system normally sized in median line; enlarged frontal cortical ditches. Conclusion: Symmetrical discrete frontal cortical atrophy.



Fig. 3. Cranial CT

Continues the treatment with Topiramate, Tonitol N, Cerebrolysin and Vitamin B12 intramuscular injected, Tanakan, Risatarun, Folic Acid, Vitamin B6, ABA therapy, follow-up in territorial CSM.

On the third hospitalization in Tg-Mures NPP Clinic (2012), we can observe the absence of epileptic seizures, on neurological examination ataxic walk but slightly improved, the mental and

psychological examination reveal the same motor stereotypies in the midline with his hands, does not use them with a purpose, psychological discontact, superficial and sporadic eye contact, hyperventilates, perioral cyanosis, rocking stereotypies. The stature weighted hypotrophy is maintained, weight: 14.5 kg at the age of 5 years.



Fig. 4. Cranial CT

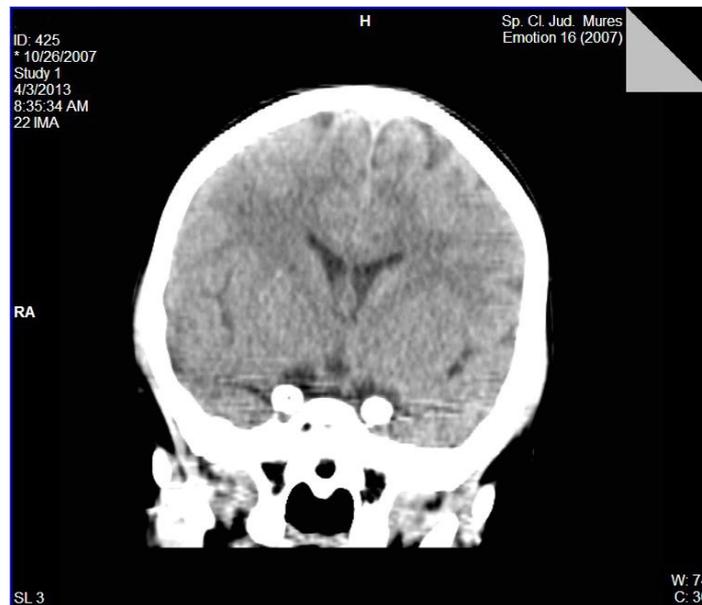


Fig. 5. Cranial CT

The diagnosis: RETT syndrome-stage III.

Differential Diagnosis

- Autism Kanner
- Atypical Autism
- Childhood disintegrative disorder

- Receptive-expressive language disorder
- Landau-Kleffner Syndrome
- Sensory deficits
- Mental retardation
- Emotional disorders in the neglected child
- Asperger Syndrome.
- Organic brain diseases accompanied by loss of mental and motor acquisitions: CNS degenerative diseases, SSPE, epileptic encephalopathies, brain tumors, etc..

Treatment: Topiramate, Vitamin B6, Folate, Vitamin B12 and Cerebrolysin im., Encefabol syrup, Tonotil N, Tanakan, multisensory stimulation, ABA therapy, special education program adapted in special kindergarten.

Conclusions: The case was interpreted as an evolutionary stage III RETT syndrome. The peculiarity of the case is that the patient presented the perinatal distress with circular cord and Apgar score 8, normal head circumference at birth, with initial corresponding development in the neuro -psycho - motor traits until around the age of 2 years.

One of the exclusion criteria in the diagnosis of RETT syndrome is ante -and perinatal distress. In this case despite suffering perinatal subsequent evolution, and also the clinical background in the hospitalizations in the NPP Clinic from Tg- Mures with evolving character to progressive degradation with loss of neuro- motor and mental autistic symptoms acquisitions lead to RETT diagnosis, in our case stage II RETT syndrome, with apparent stabilization, the patient having 5 years. In support of the diagnosis there are the symptoms of essential criteria, and also the existence of symptoms of association: stature - weighted hypotrophy, EEG abnormalities, epileptic seizures, respiratory disorder, and vegetative disorders.

In this case the diagnosis was made only clinical on the basis of the known criteria and presented by long and careful observation, unable to make a genetic diagnosis, the request being in progress, following to make this investigation in a medical institution abroad.

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CLINICAL FEATURES AND PSYCHOPHARMACOLOGICAL EFFICIENCY IN PATIENTS CLASSIFIED ACCORDING TO LESCH ALCOHOLIC TYPOLOGY

Ivanov Krasimir¹, Stoychev Kaloyan¹, Kojuharov Hristo², Donchev Tony³, Jenkov Vasil⁴, Aleksandrova Maria¹, Kirov Dimitar¹, Nakov Vladimir⁵

¹Department of Psychiatry, Medical University and University Hospital Pleven, Bulgaria

²Department of Psychiatry, Medical University and University Hospital Varna, Bulgaria

³Department of Psychiatry, Military Medical Academy Sofia, Bulgaria

⁴Department of Psychiatry, Medical University Sofia and University Hospital for Active Treatment in Neurology and Psychiatry „St. Naum”, Sofia, Bulgaria

⁵National Center of Public Health and Analyses, Sofia, Bulgaria

Abstract

Introduction: In recent decades causal heterogeneity of alcohol use disorders was widely accepted and many attempts to subclassify patients with alcohol misuse have been made. One contemporary classification is those proposed by Lesch which separates patients into four subtypes. Based on that, we made a small study exploring the characteristics of alcohol misuse and the effectiveness of different psychopharmacological drugs in a sample of patients with alcohol use disorder divided into subtypes according to Lesch typology.

Method: 44 inpatients (35 males and 9 females) with ICD-10 diagnosis of alcohol abuse or dependence admitted to Pleven University Hospital from January to December 2010 were included in the study. Patients were divided into four subtypes based on the criteria of Lesch. Mean age of sample was 44.98 years with insignificant differences between subtypes. A thorough history was obtained from all the participants focusing on characteristics of alcohol misuse (age of onset, number of hospitalizations, and severity of alcohol problems assessed with a semi-structured interview yielding a numeric score on a 9 point scale) and on psychopharmacological therapy used for relapse prevention.

Results: Subtypes II and III were most prevalent in our sample. Although Type I and type IV patients showed earlier age of onset of alcohol abuse, type II and III participants had earlier age of onset of alcohol dependence thus implying more rapid progress of alcohol misuse.

Discussion. The latter tended to run even faster in women, especially from type III. Though having fewer hospitalizations, type IV patients had the highest overall alcohol misuse severity. In terms of psychopharmacotherapy, drugs associated with longer remissions were carbamazepine [type I and II], SSRIs, trazodone [type II and III] and disulfiram [type II, III and IV].

Conclusion: Our data suggest that alcoholic patients with comorbid mood and/or anxiety disorders [type II and III according to Lesch alcoholic typology] are most prevalent among inpatient samples in our country. Disulfiram alone or in combination with antidepressants [SSRIs and trazodone] may be most beneficial for such patients.

Key words: alcohol misuse, depression, anxiety disorders, antidepressants.

¹ Correspondence: Vladimir Nakov, e-mail: vnakov@gmail.com.

Introduction

Based on the proven causal heterogeneity of alcohol use disorders, many attempts to sub-classify patients with alcohol misuse have been made in the recent years. The first classification attempts emerged in the early 1980's and utilized a two-type approach. In 1981, Cloninger suggested the dichotomy Type 1 and Type 2 alcoholism. The first one is characterized by a gradual development and an onset of dependence after 20 years of age, fewer psychosocial problems and better prognosis. The second one distinguishes an early onset of alcohol consumption with rapid development of dependence syndrome, positive family history for early onset and high severity alcoholism and is associated with marked impulsivity features. Schuckit (1985) introduced the notion of primary alcoholism (70% of the cases, early onset, male predominance, strong hereditary penetrance) and secondary alcoholism (later onset, subjacent psychopathology such as mood and/or anxiety disorders). Babor et al. (1992) elaborated the distinction between alcoholism Type A, with late onset of alcohol-related problems and better prognosis, and Type B, characterized by early onset, marked childhood behavioral problems, family history of alcoholism, severe dependence syndrome, and psychopathological comorbidity.

Hauser and Rybakowski (1997) based on K-means cluster analysis delineated three subtypes of alcoholic males: Type 1 characterized by late onset of alcohol dependence, low prevalence of family history of alcoholism, and mild severity of the pathology course; Type 2 characterized by early onset of alcohol dependence, high prevalence of parental alcoholism, antisocial personality, and severe alcohol-related problems; and finally Type 3 characterized by early onset of alcohol dependence, family history of psychiatric diseases, severe alcohol-related problems, and high prevalence of psychiatric disturbances and somatic diseases.

Lesch et al. (1988, 1996) and recently Windle and Scheit (2004) introduced a four-type solution of alcoholism. Lesch et al. (1988, 1996) distinguished four evolutionary types depending on the family history of alcoholism, previous personal psychopathology, and neurobiological substratum. Thus, *Type 1* consists of patients with heavy withdrawal symptoms and strong craving which is presumably due to genetically based brain reward circuitry vulnerability. *Type 2* patients are characterized by high anxiety and neuroticism as personality traits, probable abnormalities in brain serotonergic systems and tendency to abuse alcohol because of its anxiolytic effects. The main feature of *type 3* patients is an underlying affective disorder, most often depression. In this type, abnormalities in chronobiological brain systems are hypothesized. *Type 4* patients have premorbid cerebral defects and cognitive impairment and the course of their alcohol misuse is characterized by severe psychosocial deterioration and poor outcome as a rule. Windle and Scheit (2004) using a cluster analytical procedure identified four alcoholic subtypes: *Mild course* - later alcohol onset; fewer years of drinking; lower levels of alcohol consumption; lack of severe withdrawal symptoms;

least childhood conduct problems; lowest family history for alcoholism. *Polydrug* - highest levels of polydrug use, symptoms of major depression, generalized anxiety, and/or personality deviations. *Chronic/ASP* - high levels of alcohol consumption and adult antisocial behavior.

In Portugal, Cardoso et al. (1997; 2006) based on factorial analysis of outpatient samples have proposed a five type model with the following subtypes: *Anxiopathic type* – represents a group whose alcoholic behaviors are precipitated by anxious personality traits; *Heredopathic type* - personifies a pattern of early onset of alcohol consumption, father alcoholism background, verbal aggressiveness and/or suicidal tendencies during alcohol consumption; *Thymopathic* - reveals a psychopathological profile of clinically significant anxiety and/or depressive disorder. In these individuals alcohol consumption is used as a form of self-treatment of negative affects. *Sociopathic* - typifies a profile with a high level of dependence, marked aggressiveness and social non-compliance as a stable personality trait (which may become excessive when consuming alcohol) and deep social repercussion of alcoholic consumption (legal problems etc). *Adictopathic* - similarly to the sociopathic type, this subtype comprises younger individuals with disruptive behavior consuming other types of psychoactive substances besides alcohol.

In the last decade intensive research is being conducted focused on finding the most effective relapse preventing medications for different subtypes of alcohol misuse patients. For example, Dundon et al. (2004) found more favorable treatment outcomes for Babor's Type A alcoholics when treated with sertraline. Comparing abstinence rates, Kiefer et al. (2005) found that acamprosate was mainly efficacious in patients with low baseline somatic distress, whereas naltrexone was effective especially in patients with high baseline depression. As for Lesch's typological differentiation, there is preliminary data that different subtypes of patients tend to respond to specific pharmacotherapeutic relapse prevention approaches (Hillemacher & Bleich 2008, Lesch et al. 2001). Thus, Type 1 patients are likely to benefit from Disulfiram, Acamprosate, Gammahydroxy-butyric acid or Nalrtexone. Recommended therapies for type 2 are acamprosate, antidepressants (moclobemide and trazodone) and Gammahydroxy-butyric acid. Type III patients would require adequate antidepressant treatment when in clinically significant depression (TAD, SSRI or SNRI in severe forms or Trazodone in mild depression may be used) and naltrexone for relapse prevention. Gammahydroxy-butyric acid may be used in early relapse stages. Regarding type IV patients, naltrexone combined with Gammahydroxy-butyric acid produces best results, although treatment is least successful in this subgroup.

Based on the abovementioned data, we made a small study exploring the characteristics of alcohol misuse and the effectiveness of different psychopharmacological drugs in a sample of patients with alcohol use disorder divided into subtypes according to Lesch typology.

Method

44 inpatients (35 males and 9 females) with ICD-10 diagnosis of alcohol abuse or dependence admitted to Pleven University Hospital from January to December 2010 were included in the study. Socio-demographic characteristics of patients are presented in Table 1. Individuals with severe somatic diseases and also those with organic psychiatric disorders were excluded from study.

Table 1. Social-demographic characteristics of the sample

Characteristic	Total (n=44)	%	Females (n=9)	%	Males (n=35)	%
Age (yrs + SD)	44.98 ± 7.85	-	36.11 ± 6.23	-	46.59 ± 6.80	-
Marital status						
- Single/divorced/widowed	23	52.3	5	55.5	18	51.4
- Married	21	47.7	4	44.5	17	48.6
Occupational status						
- Employed	22	50.0	5	55.5	17	48.6
- Unemployed/retired	22	50.0	4	44.5	18	51.4
Residence						
- Small town/village (<20 000 cit.)	21	47.7	5	55.5	16	45.7
- Principal town (>20 000)	23	52.3	4	44.5	19	54.3
Education						
- Secondary	28	63.6	4	44.5	24	68.6
- Higher (college, university etc.)	16	36.4	5	55.5	11	31.4

Patients were divided into four subtypes based on the criteria of Lesch et al. (1) using a specially designed software (Lesch Alcoholism Typology, ver. 3.0.20, Bulgarian language). A thorough history was obtained from all the participants focusing on characteristics of alcohol misuse (age of onset, number of hospitalizations, number and length of remissions, severity of alcohol problems etc.) and on psychopharmacological therapy used for relapse prevention. For eliciting alcohol misuse and psychiatric history we used a structured diagnostic interview – Mini International Neuropsychiatric Interview Plus ver. 5.0.0. (Sheehan et al. 1998). To enhance data reliability, all patients' histories were verified by additional medical documentation and/or interviews with relatives. In patients with comorbid mood or anxiety disorders, temporal relationships between alcohol misuse and mood and/or anxiety symptoms (i.e. determining which is primary and which secondary by examining the age of onset of both disorders) were explored by using the chronological method of Schuckit et al. (1997). Severity of alcohol problems was assessed by Addiction Severity Index, European version (Kokkevi and Hartgers, 1995). This semi-structured interview has a built-in 9 point scale which serves to grade the magnitude of alcohol problems.

Results and discussion

Our main findings are briefly summarized in the Table 2.

The four separate subtypes showed insignificant differences in terms of mean age (approx. 44.5 years). Female patients as a group however, showed substantially lower mean age compared to males (36.11 years vs. 46.59 years). Lesch's subtypes II and III were most prevalent in our sample. Such findings are not surprising given the fact that type II and to a lesser extent type III represent an

equivalent to Cloninger et al. (1981) “Type 1” alcoholism, Schuckit (1985) “secondary alcoholism” and Babor et al. (1992) “Type A” alcoholism. Although some leading researchers believe that alcohol dependence with early onset, male predominance and strong hereditary component represents the majority of cases, some recently published data show that factors as anxiety and emotional instability (neuroticism) which are personality traits that are strongly expressed in patients with Lesch subtype II and III alcoholism, explain substantial part of the total variance of alcohol related behaviors (Cardoso et al. 2006). Another possible reason for the predominance of Type II and III cases in our sample is the fact that it includes only hospitalized patients. It is well known that alcohol abusing and dependent individuals who have co-occurring mood and/or anxiety symptoms are much more likely to seek treatment and thus are usually overrepresented in inpatient samples – phenomenon known as “Berkson bias” (Berkson 1946; Hintz & Mann, 2005).

Table 2. Results of the study

Patient subtype	Number of patients (males/female)	Mean age of onset of alcohol abuse (years)	Mean age of onset of alcohol dependence (years)	Mean number of hospitalizations	Overall alcohol misuse severity score	Number of patients with long (>6 months) remissions
I	4 (4/0)	33.25	41.00	3.00	6.75	2
II	17 (14/3)	37.88	40.17	2.06	6.44	8
III	19 (13/6)	34.05	38.00	3.05	6.28	14
IV	4 (4/0)	33.25	47.00	1.75	7.75	2

As for the beginning and course of alcohol problems, although Type I and type IV patients showed earlier age of onset of alcohol abuse, type II and III participants had earlier age of onset of alcohol dependence thus implying more rapid progress of alcohol misuse. The latter tended to run even faster in women, especially from type III. Besides providing a possible explanation of the abovementioned lower mean age of the women in our sample, this finding is in agreement with the so-called „telescopic effect phenomenon” in female alcoholism described in literature (Hallman et al. 2001; Blume, 2003). Though having fewer hospitalizations, type IV patients had the highest overall alcohol misuse severity thus rendering our data in accordance with similar findings of other authors (Lesch et al. 1996; Hillemacher & Bleich 2008).

In terms of psycho-pharmacotherapy, drugs associated with significant remissions (longer than 6 months) were carbamazepine (type I and II), SSRIs, trazodone (type II and III) and disulfiram (type II, III and IV).

Conclusion

In agreement with other authors (Windle and Scheidt 2004, Cardoso et al. 2006), we believe that a four- or five-subtype resolution, rather than two, offers a more useful multidimensional classificatory approach for the heterogeneity of alcoholic behaviours, providing a helpful guiding

research for optimized treatment matching strategies. Our data suggest that alcoholic patients with comorbid mood and/or anxiety disorders (type II and III according to Lesch alcoholic typology) are most prevalent among inpatient samples in our country. Disulfiram alone or in combination with antidepressants (SSRIs and trazodone) may be most beneficial for such patients. To verify this data, more studies comprising larger samples are needed.

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CHILD AND ADOLESCENT MENTAL HEALTH FROM A GLOBAL PERSPECTIVE: THE CASE OF ALBANIA

Sonila Tomori¹, Agim Gjokopulli¹, Ariel Como², Eugjen Sotiri².

¹Tirana University Hospital Center "Mother Tereza", Pediatric Service 2, Albania

²Tirana University Hospital Center "Mother Tereza", Psychiatric Service, Albania

Abstract

The objective of the article is to present the situation of child and adolescent mental health in one the South-East European countries, Albania, on the light of needed measures and activities for a potential scaling up of the intervention offer in a context of limited resource country. It represents an attempt for bringing the concepts formulated as part of Global Mental Health approach for low and middle income countries on the specificities and context of a particular country. Locally produced data are presented in support of the concept that future developments in such settings should start by a) empowering pediatricians and school environment, b) boosting research since the beginning in two directions: adapting and validating screening instruments for being used by primary health care professionals and pediatricians, and implementing prioritizing research exercise, c) strengthening the evidence-based approach of existing treatment service and establishing new ones in different parts of the country.

Key words: *child and adolescent mental health, systems of care, global interventions, low-income countries.*

The global perspective

Poor mental health in childhood and adolescence is a prevalent global public health challenge and accounts for a significant proportion of the disease burden and disability among age groups worldwide. The vast majority of children in Low and Middle Income Countries (LMIC) do not have access to the interventions (Patel, 2013).

While worldwide prevalence of child and adolescent mental disorders is approximately 20%, from 4-6% are in need of a clinical intervention for an observed significant mental disorder (WHO, 2005, 2001). The magnitude of mental health problems has not yet been recognized sufficiently by many governments and decision-makers (Renschmidt, 2005).

Little is known about child mental disorders – their epidemiology, phenotypes, etiology or treatment – from LMCI (Patel, 2013). The large resource gap for child mental disorders, arguably even larger than the widely recognized gap for adult mental disorder, is mirrored in the evidence

¹ Correspondence: Sonila Tomori, e-mail: s_tomorius@yahoo.com

gap (Patel, 2007). A disproportionately large percentage of the 'burden of disease as calculated by WHO, falls in the category of 'neuropsychiatric conditions in children and adolescents' (Renschmidt, 2005).

Research which aims to improve access to care for child mental disorders emerged as one of the leading Grand Challenges in Global Mental Health (Collins, 2011).

The recent mhGAP guidelines (WHO, 2010), testify to the effectiveness of a range of pharmacological and psychosocial interventions for these disorders (Patel, 2013), but as for the mental health in general, the availability of basic medicines for mental disorders in primary health care is notably low (in comparison to medicines available for infectious diseases and even other non-communicable diseases), and their use restricted because of the lack of qualified health workers with the appropriate authority to prescribe medications. In addition, the availability of non-pharmacological approaches and trained personnel to deliver these interventions is also lacking. Such factors act as important barriers to appropriate care for many persons with mental disorders (WHO, 2013).

Developmental disabilities (such as intellectual disability and autism), emotional disorders (notably anxiety and depression), and disruptive behavior disorders (notably conduct disorder and ADHD) are the leading mental health related causes of the global burden of disease in children aged below ten years (Patel, 2013).

Albania situation

Child and Adolescent Mental Health is recognized as one of the priority issues on the newly formulated (soon-to-be published) 2013-2020 mental health action plan of the Health Ministry, pointing out the need for further elaboration of strategic documents in the years to come. Referral to human rights universal treaties is also offered.

The processes of developing WHO Mental Health Action Plan 2013-2020 (WHO, 2013) had its influences on country-based formulations. The WHO document states that "Policies, plans and services for mental health need to take account of health and social needs at all stages of the life course, including infancy, childhood, adolescence, adulthood and older age". Further it highlights that "A comprehensive and coordinated response for mental health requires partnership with multiple public sectors such as health, education, employment, criminal justice, housing, social and other relevant sectors as well as the private sector".

The WHO Mental Health Atlas 2011 (WHO, 2011) shows that in the country there are 1.83 psychiatrists, 0.63 medical doctors not trained in psychiatry, 6.18 nurses, 1,29 psychologists, 1.1 social workers, 0.09 occupational therapists for 100000 inhabitants. No information in regard to child and adolescent mental health might be found.

Today, the child and adolescent public services in the country are quite limited, all of them in the country Capital city accounting for a few tenths of buildings rooms: the largest is a 12 staff members' clinic (4 psychiatrists, 2 psychologists and 6 nurses at the University Hospital offering outpatient and inpatient services (15 beds), 2 sections of 4-5 staff members within general mental health community mental health centers, a liaison psychiatrist and a psychologist at pediatrics clinic in University Hospital. Some mental health service is offered also within a National Growth and Development Center. Although systemized data is missing, the number of children and adolescents enrolled in all services annually receiving single or multiple sessions intervention counts to about 4000, (less than 0,4% of country child and adolescent population) most of them on the range of less than 5 sessions. Quite often, the primary drive to reach mental health services is the social service system request of applying for disability pension. Evaluation and Diagnostic, and medical follow-up remain the big slice in what mental health facilities are presently offering.

Although not studied, stigma, awareness and level of knowledge on mental health throughout health system of care are believed to be main barriers. Indirect costs, such as traveling and loss of working days for parents are important barriers too.

Public specialized programs specific for behavioral problems, learning disabilities, speech and language delays are missing. Non-governmental organizations, often heavily relying on ups-and-downs of international flow of international donations and charities fulfill modestly the gap.

Within the health system the average time of reaching specialist care after first visit to primary health care facilities is less the one month, but the length of time spent in informal circles of 'traditional healers' often reach years. No publication or reference describing child and adolescent services in the country.

Since 2003 a postgraduate training program in child and adolescent psychiatry designed considering the recommendations of the Section of Child and Adolescent Psychiatry within the Union of European Medical Specialists (UEMS) is in place in the only countrywide institution offering postgraduate programs, Tirana Medical School of Medicine, but only 5 are completing the program since, while 7 more will accomplish it by 2015. Local capacities for implementing the program-content on the standards of UEMS are a different issue from the paper-program.

A juvenile justice system for delinquent children and adolescent is missing despite often-spoken initiatives of governmental bodies and international assistance agencies to deal seriously with the issue. Media-covered cases of criminal activity including tens and adolescents are frequent as it is of suicide in this age-group.

Initial attempts for service data-collection in mental health have started lately, while epidemiological data collection system is missing.

The Essential Drug list for the Primary Health care includes at least one medicament from tricyclics, SSRI's, antipsychotics, mood stabilizers and anxiolytics, but no psychostimulants. In practice, quite often families have to use the out-of pocket money for securing the prescribed medicaments.

Attempts for including psychosocial and family based interventions in the existing service settings have an increased trend in the last years, especially by enrollment in mental health facilities psychosocial staff, but it all remains far from being structured and systematic.

Children and adolescents represent 8% of patients treated yearly in outpatient facilities, 25% of those in day treatment facilities and 3% of admissions in general hospital (Albanian Institute of Public Health, 2010). The WHO led survey in 42 LMIC that used the WHO Assessment Instrument for Mental health systems estimated that children and adolescents make up only 12% of the patient population in mental health outpatient facilities and less than 6% in all other types of mental health facilities (Morris, 2011).

The health system in Albania is mainly public. The state is the major provider of health services, health promotion, prevention, diagnosis and treatment. The private sector, which is still developing, covers most of the pharmaceutical and dental services, as well as some clinics for highly specialized diagnosis, mostly in Tirana (Albanian Institute of Public Health, 2010). Children constitute more than a third of the Albanian population, with a number of 1,048,702 out of the 3,194,417 inhabitants of Albania (Albanian Institute of Statistics, 2011). A 2011 census shows that for the first time the population in urban area is larger, 53.7% (Save the Children, 2012), than rural areas.

What for the future: combating stigma, task-sharing, role of pediatricians and primary health care

The main problems of mental health care for children and adolescents in Albania are related with level of stigma, inadequate funding for public mental health services especially those for child and adolescent mental health resulting in a very limited range of typology of services available, and a very large treatment gap, while preventive programs are rudimentary. The treatment gap leaves space, or at least, cannot serve as proper alternative to informal traditional healers, flourishing in part of the country, mainly rural.

The shortage of human resources in child and adolescent psychiatry is evident in LMCI countries. The massive shortage of specialized human resource is unlikely to be bridged in the foreseeable future (Patel, 2013).

In light of the evidence and analyses presented in the Patel et al. article on the global perspective on improving access to care for children with mental disorders, a number of ideas for moving ahead in low-resources countries offer clear guidance for formulating the directions of a possible 'what to do' in Albanian context:

- Interventions to reduce the burden of mental disorders in children typically include a range of promoting, preventive and treatment strategies. While the former usually refer to interventions aiming to avoid the incidence, the latter are directed to established disorder.

- The age-group of children under the age of nine years encompasses distinct, if overlapping, developmental phases which are associated with different types of mental disorders and different strategies for improving access to intervention.
- The approaches to the delivery of evidence based treatments for child mental disorders would need to take a very different strategy to the specialist-led model adopted by well resourced countries.
- Such strategies would need to adopt the principles of task-sharing, widely used in other areas of global health and in adult mental health.
- Working in collaboration with pediatricians and training pediatricians in mental health interview and evaluation techniques, recognition and diagnosis of behavioral has been found to increase mental health diagnoses in pediatric practices as any attempt in developing countries to identify and treat these disorders will be incomplete unless pediatricians are involved in the process.
- School based policies and programs coupled with increased awareness amongst parents and collaborative support and referral pathways from trained mental health personnel as in optimal circumstances, community-based care needs to be coordinated with school based and clinical based services.

While the overall number of general practitioners in Albania is on the level of 2000, the specialized physicians on the level of 1500, a third of the latter are pediatrician. These are the first point of contact (and often the only) for the child and adolescent population in the country. But information, knowledge and tools would be needed to enroll properly them in mental health care aspects.

There are two positive samples in the country of impact on pediatric institutions on increasing the detection of mental disorders and the integrated care offer. The first is enrollment of psychiatrists in the National Child Growth and Development Center, while the second, the inclusion of a psychiatrist at the Pediatric Service of the University Hospital. In both cases the number of mental disorders identified by pediatricians increased essentially.

Inclusion of psychologists in health institutions is a positive trend of the last years in the country. Together with pediatricians they are a natural possible target for being important allies for working with children and adolescents with mental disorders.

The number of psychologists serving as school councilor is also in rise. Although presently overloaded with routine work, they are another possible target for being important actors in the identification and referral, besides promoting and preventive role they have in their natural role.

The enlargement of existing service and development of new ones in other parts of the country besides the capital remain of paramount importance. Placing from the beginning an adequate evaluation system of efficacy and cost effectiveness becomes as important as offering evidence based interventions and integrative approach with social and educational systems.

The WHO's mhGAP intervention Guidelines, could be a very important tool.

Stigma and a lack of awareness about mental health problems are important contributors to a relatively low demand for services. Among populations where stigma is high and knowledge level low, efforts should be directed in the first instance to increasing general awareness. Programs aiming to increasing general awareness would be highly needed in the country. School is a particularly important setting for stigma reduction and information raising activities (Flisher, 2010).

Research for scaling up

Proper treatment of mental and developmental disorders rely mostly on early identification, which on the other side needs screening programs and screening tools. In a country where such instruments are missing this might be considered high in the list of priorities. Combined with awareness rising programs for primary health care staff and pediatric settings it might start influencing the overall attitude towards growth and development as concepts overcoming old medicine of weight, height and vaccines for the physical well-being. Developmentally appropriate and culturally sensitive instruments are needed to be the first step in diagnosis (Mahfoud, 2011).

An established research agenda accompanying each step of interventions design and implementation might be considered a sound priority. Barriers in this regard are multidimensional too. Human and financial resources are important, but they are not the only ones. The clinical practice in medicine is often offered based on approaches other than evidence-based, while the health facilities and institutions are routinely managed and administered without specific attention towards measuring effectiveness and efficiency. As such, policy-making based on data has not a strong tradition.

Prioritization of mental health research is a critical component in the process of scaling up of services for mental health (Sharan, 2009). Developing a local agenda which is driven by the necessity of feeding service development process and evidence-based intervention models, combined with efforts to increase funding and skilled workforce, will have to be a necessity for securing sustainable solutions and developments.

The research in mental health is very limited in Albania. Quite often the implemented research projects were designed either on the criteria of being accomplished without specific funding, using the data coming from patients records in clinic settings, or in accomplishment of the agenda of an international agency or organization.

A prioritizing research exercise for the country, and largely for the region would be needed not only on the service of planning and evaluation of services in the country, but also for assisting international work in the field when it is possible.

On the regional perspective

Research prioritization exercise and developing culturally validated instruments for screening and early identification seems being challenges for most countries in the region.

As such, these might be areas of feeding partnerships and collaborations too. Scaling up service offer in countries like Albania clearly needs efforts and investments in a number of dimensions. The needed pool of institutional, organizational, and professional knowledge is hard being found only on books and journals. Building partnerships with outside country actors should be considered priority activity.

It is not difficult to see that different LMIC countries, besides specificities have many similar challenges, while for some more developed countries similar challenges have been posed only a few years ago. Countries in the south-east Europe might find huge areas of mutual exchanging experiences and lessons learned. Early prevention and early identification, stigma, service information data production and analyses, cross-sector collaboration and team work, but especially research activities are most probably a common language. Regional or larger partnership building is also related to capacities, knowledge and investment. Technology is making possible intensive communication. It is a tool mental health professionals in this part of world might make use for reaching many of the objectives posed and embedded already.

Some conclusions

Child and adolescent mental health represents an area of huge services gap in a country like Albania. Recent developments globally resulting in a focused attention towards child and adolescent mental health offer a momentum for elaborating and pushing towards local and regional developments: locally to use the concepts and formulations elaborated from a global perspective in adapting steps and measures appropriate for the context; regionally for establishing and strengthening partnerships and collaborations. Technology advances offer excellent chances for intensifying exchange of information, building training and treatment opportunities as well as moving easier away with regionally designed agendas. Research activities are limited in countries like Albania, counting maybe for one of the factors why the child and adolescent mental health system of care remains underdeveloped.

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QUALITY OF LIFE ASSESSMENT IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER ASSOCIATED WITH TYPE 2 DIABETES MELLITUS

Cristian Gabos Grecu¹, Elena Gabriela Buicu^{1,3}, Theodor Moica², Melinda Ferencz^{1,2},
Florin Buicu¹, Cosmin Octavian Popa³, Iosif Gabos Grecu^{1,2}

¹University of Medicine and Pharmacy, Tirgu Mures, Romania

²Psychiatric Clinic No 1, Tirgu Mures, Romania

³Mental Health Center, Tirgu Mures, Romania

Abstract

Introduction: Diabetes mellitus (DZ) is a common chronic disease characterized by absolute or relative deficit of insulin, hyperglycaemia and short time/long time complications. The abnormalities that define type 2 diabetes mellitus are represented by the presence of insulin resistance and insulin deficiency due to a defective secretion of insulin. According to WHO data, 280 million of people are diagnosed with diabetes mellitus in the world nowadays and 55.2% of them live in Europe.

Materials and methods: The research was carried out at MEDIAB Centre of Targu Mures in collaboration with the specialised ambulatory of Psychiatric Clinic No. 1, during September 2012 – April 2013, for 180 patients recorded by the diabetologist, diagnosed with type 2 diabetes mellitus. For the assessment of the presence/absence of the depressive disorder during the first stage we used the Anxiety and Depression Scale (Hospital Anxiety and Depression Scale) (Keedwell and Snaith, 1996). Dr. Radu Teodorescu translated it for the first time to Romanian and published it the Sinapse magazine (1996).

Discussion: The studies on patients with depressive disorder also showed a high rate of comorbidity with type 1 or 2 diabetes (12). The results of several studies on patients with diabetes found that depressive disorder in diabetes affected patients is often untreated and incorrectly rated, and that this appears to be a symptom of recurrence (14).

Conclusions: Depressive disorder comorbid to diabetes mellitus associates with a lower quality of life. The coexistence of depressive symptoms and of the basic chronic disease contributes to a lower quality of life, which is why greater attention to identifying and treating these coexisting psychiatric problems is needed, in order to reduce their negative impact on the quality of life.

Key words: diabetes, depression, quality of life.

¹ Correspondence: Florin Buicu, Maramures St., no. 10, Tirgu Mures, Romania.
Tel.: +40 740 031202, e-mail: florin_buicu@yahoo.com.

Introduction

Diabetes mellitus (DZ) is a common chronic disease characterized by absolute or relative deficit of insulin, hyperglycaemia and short time/long time complications. The abnormalities that define type 2 diabetes mellitus are represented by the presence of insulin resistance and insulin deficiency due to a defective secretion of insulin. According to WHO data, 280 million of people are diagnosed with diabetes mellitus in the world nowadays and 55.2% of them live in Europe. According to the prognostics, this number will increase up to 380 million in the following 20 years, fact that represents a major health concern in the whole countries (5). Type 2 diabetes is the most spread type of diabetes and is more common for Americans, Afro-Americans, Latins and Asians and, generally for people over 45 years old (8).

In Romania, the prevalence of diabetes mellitus was 1.98% in 2003, it increased up to 2.12% in 2004 and up to 2.23% in 2005, and there were recorded 429,979 patients in 2003, 459,518 in 2004 and 482,250 in 2005. According to the data of the Ministry of Health, there were 50,062 new cases in 2003, 54,561 in 2004 and 53,443 in 2005, with an incidence of 230 for 100,000 inhabitants in 2003, 251 in 2004, 247 in 2005, 336.1 in 2009 and 319.1 in 2010 (16).

Many studies have shown that comorbid depression associated with diabetes mellitus increases the use of medical services and implicitly the costs.

According to WHO, the direct costs of the diseases related to diabetes represent 2.5% - 15% of the country's annual budget allocated for healthcare and depends both on the local prevalence of diabetes and on the degree of the available treatments. In Romania, they allocated a budget of 90 million euro in 2006, which represent about 2% of the total budget allocated for healthcare in that year (16).

The latest epidemiological studies have shown that patients with diabetes mellitus have a higher risk to experience one or more depressive episodes during their lives (7).

Aim

To investigate the relation between the depression and the quality of life in patients with type 2 diabetes mellitus that are recorded by a diabetologist, in ambulatory.

Method

The research was carried out at MEDIAB Centre of Targu Mures in collaboration with the specialised ambulatory of Psychiatric Clinic No. 1, during September 2012 – April 2013, for 180 patients recorded by the diabetologist, diagnosed with type 2 diabetes mellitus. For the assessment of the presence/absence of the depressive disorder during the first stage we used the Anxiety and Depression Scale (Hospital Anxiety and Depression Scale) (Keedwell and Snaith, 1996). Dr. Radu Teodorescu translated it for the first time to Romanian and published it the Sinapse magazine

(1996). Dr. Maria LADEA validated it in her PhD thesis for Romanian psychiatric patients. In the second stage, the 36 patients that got over 11 points in HADS scale, were directed to the ambulatory of the Psychiatric Clinic. After a specialised assessment they were diagnosed with major depressive disorder according to the DSM – IV- TR diagnosis criteria. In order to assess the severity of the depression we used 17 items Hamilton scale. From the group of 144 patients with type 2 diabetes mellitus, we chose 36 patients with type 2 diabetes mellitus and with similar demographic data like the 36 patients with diabetes mellitus and depression. During the third stage we gave the patients the Quality of life assessment questionnaire and we asked them to point out the quality of their lives during the last month. Please answer to the following questions according to the following scale: During the last 4 weeks did you have one of the following problems related to the place of work or to other daily regular activities, as a result of your physical or emotional condition? 0 – not at all/excellent; 1 – little/very good; 2 – somehow/good; 3 – moderate/acceptable; 4 – hard/bad;

1. Did you reduce the time spent for work or other activities?
2. Have you realized less things than you wished?
3. Do you think that your working time or activities were limited?
4. Was it difficult to carry out your work/activities (do they need an additional effort)?
5. Generally, can you say that your health condition at the moment is?
6. How do you appreciate your health condition now in comparison with the health condition that you had 3 months ago? How did your physical condition affect your social activities together with your family, friends, neighbors or social circles during the last 4 weeks? How much did pain affect your usual work (including work outside the house and household work) during the last 4 weeks?
9. How much did weakness or tremble did affect your usual work (including work outside the house and household work) during the last 4 weeks?

We also gave the patients the SDS, (Sheehan et al., Disability questionnaire. The measurement of disability; International Clinical Psychopharmacology 1996; 11:89-95). SDS is a self-assessment scale, in which the patient reports the functional disability and the dysfunctionality, during the last week, due to psychiatric symptoms.

For the interpretation of the statistical data we used the GraphPad Prism 6 statistics programme for Windows and Excel tables. From the statistical point of view, for the interpretation of data we used the t test for two samples of correlated/related scores. In this research we used the “t test” that compares the scores obtained in the same sample, known as the “t test for pair samples. In order to check the normal (Gaussian) distribution of data we used the concordance Kolmogorov-Smirnov and D'Agostino-Pearson's tests. They helped us to point out the type of frequency of our sample. These concordance tests identify if a sample comes from a statistical population that comply with a certain type of frequency distribution.

Results

36 patients that represent 20% of the 180 patients recorded by the diabetologist with type 2 diabetes mellitus were diagnosed with depression associated to diabetes (Fig. 1).

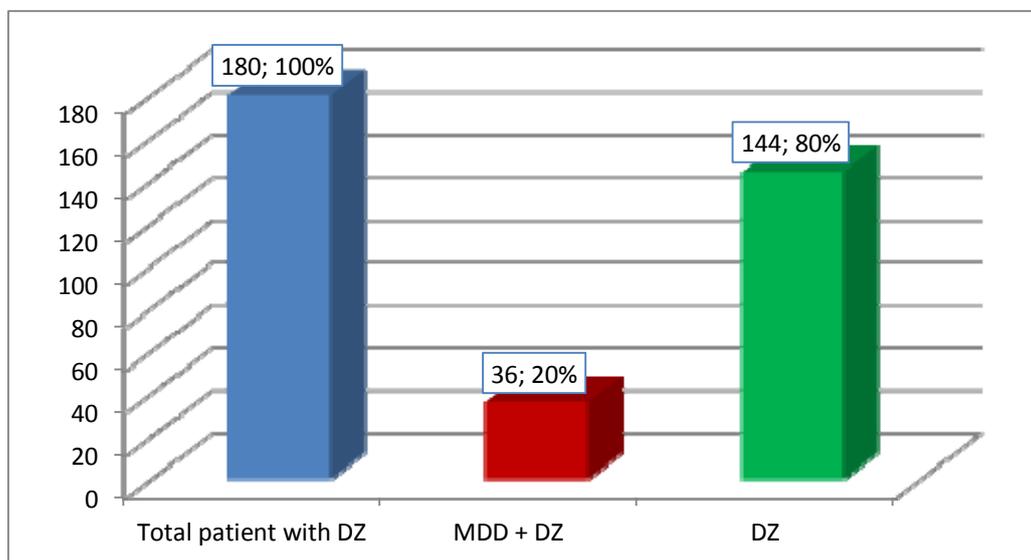


Fig. 1. Distribution of patients with MDD and DZ

The sample of patients that have depression and diabetes is made up of 24 females and 14 males and the age average is $M_{age} = 59.75$ years old. The sample of patients with diabetes is made up of 26 females and 10 males and the age average is $M_{age} = 61.39$ years old (Fig. 2 and 3).

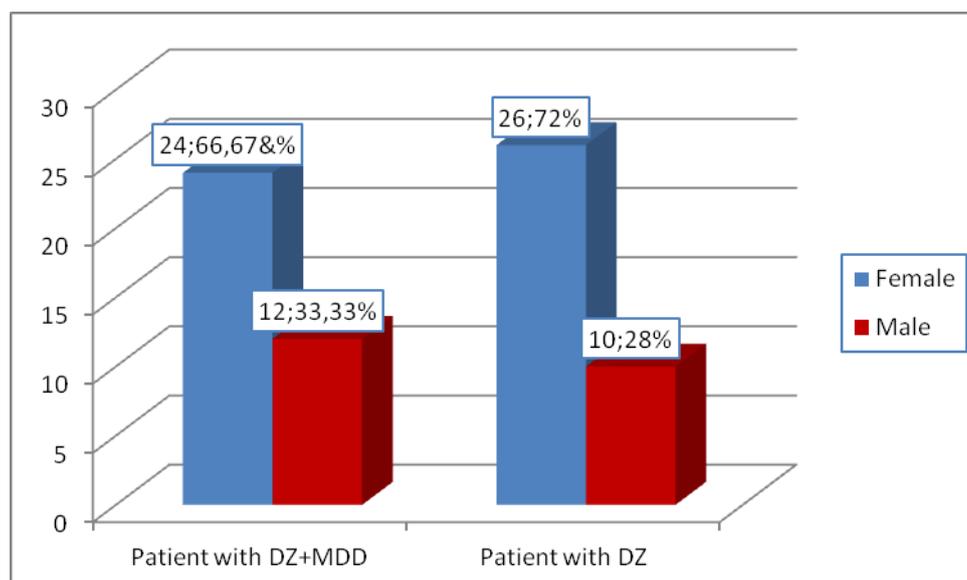


Fig. 2. Distribution of patients with MDD and DZ depending on sex

From the point of view of the origins, in the sample of patients with depression and diabetes 8 of them came from the rural environment and 28 from the urban environment and in the sample of patients with diabetes, 10 of them came from the rural environment and 26 from the urban environment.

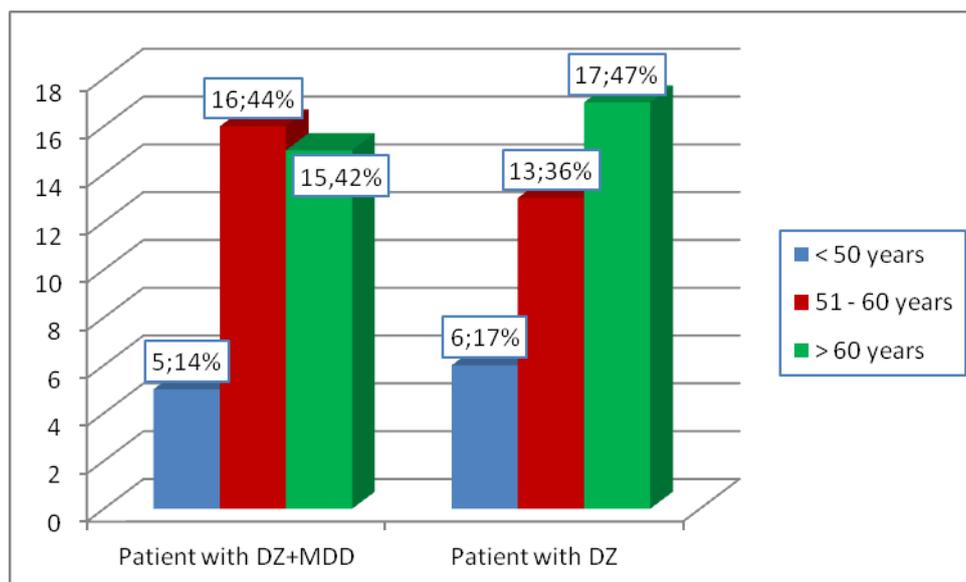


Fig. 3. Distribution of the 2 samples depending on age

From the point of view of the medication, in the sample of patients with depression and diabetes, 22 patients were taking oral antidiabetic medication and 14 patients were taking both oral antidiabetic medication and insulin and in the sample of patients with diabetes, 24 patients were taking oral antidiabetic medication and 12 patients were taking both oral antidiabetic medication and insulin (Fig. 4). In what regards the antidepressant medication, in the sample of patients with depression and diabetes, 18 patients were taking Duloxetine – 60 mg dose and 18 patients were taking SSRI.

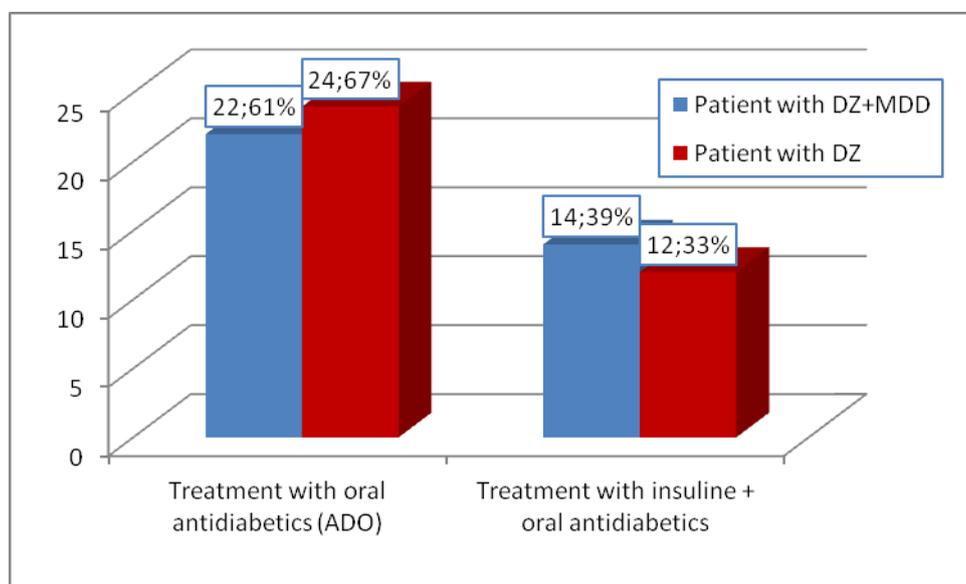


Fig. 4. Distribution of the two samples depending on the antidiabetic medication

From the point of view of the duration of the main disease (type 2 diabetes mellitus), in the sample of patients with depression and diabetes: 12 patients (33.33%) were diagnosed with diabetes since less than 2 years ago, 15 patients were diagnosed since 2-5 years ago (41.66%) and 9 patients (25%) were diagnosed since more than 5 years. In the sample of patients with diabetes: 14 patients

(38.88%) were diagnosed with diabetes since less than 2 years ago, 16 patients were diagnosed since 2-5 years ago (44.44%) and 6 patients (16.66%) were diagnosed since more than 5 years.

If we study the impact of diabetes on the quality of life in the sample of patients with diabetes (Fig. 5) we have higher scores at the whole items of the quality of life questionnaire, fact that means the reduction of the quality of life. The score average was around 22.33. After 6 months, during which patients kept taking antidiabetic medication, we reassessed the impact of diabetes on the quality of life and we got similar results, and the score average was 21.02.

We assessed the impact on the quality of life in the group of patients with diabetes and depressive disorder (Fig. 6) and obtained high scores in all quality of life questionnaire items, which means a significant lower quality of life. The mean scores were around 29.33. After 6 months, period in which the patients continued the anti-diabetic and antidepressant treatment (Duloxetine and SSRI), we re-assessed the impact of depression and diabetes on the quality of life, and we observed a 50% lowering of the scores of all the items of the questionnaire on the quality of life, which means an improvement of the quality of life, with mean scores of 11.16.

We assessed the impact of the psychiatric symptoms on the quality of life in patients with diabetes and depressive disorder both at baseline and after 6 months, using the SHEEHAN disability scale, with the patient reporting the functional incapacity and disability in the previous week (Fig. 7). We obtained high scores in all items, which means a significant lower quality of life. The mean scores were around 35.27, surpassing the mean scores of the quality of life questionnaire in patients with diabetes. After 6 months, during which the patients continued the antidiabetic and antidepressant treatment (Duloxetine and SSRI), we reviewed the impact of the psychiatric symptoms on the quality of life, noticing a 70% decrease of all the scores of the quality of life questionnaire items, which means an improvement of the quality of life, with mean scores of 8.19.

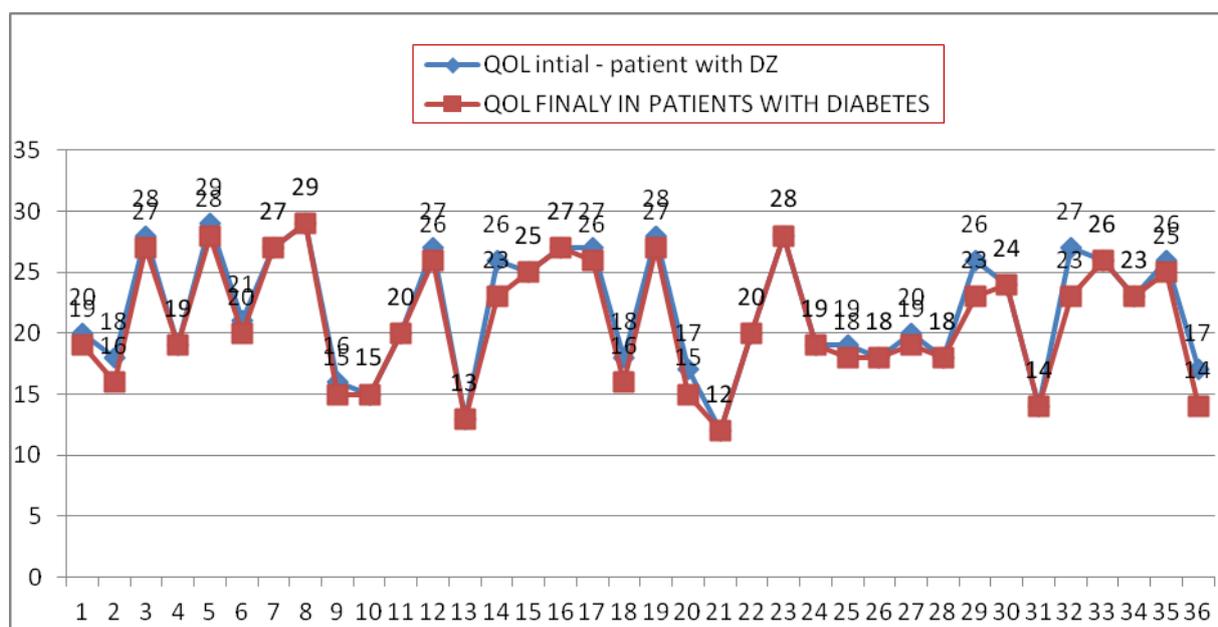


Fig. 5. QOL baseline results and after 6 months – The group of patients with diabetes

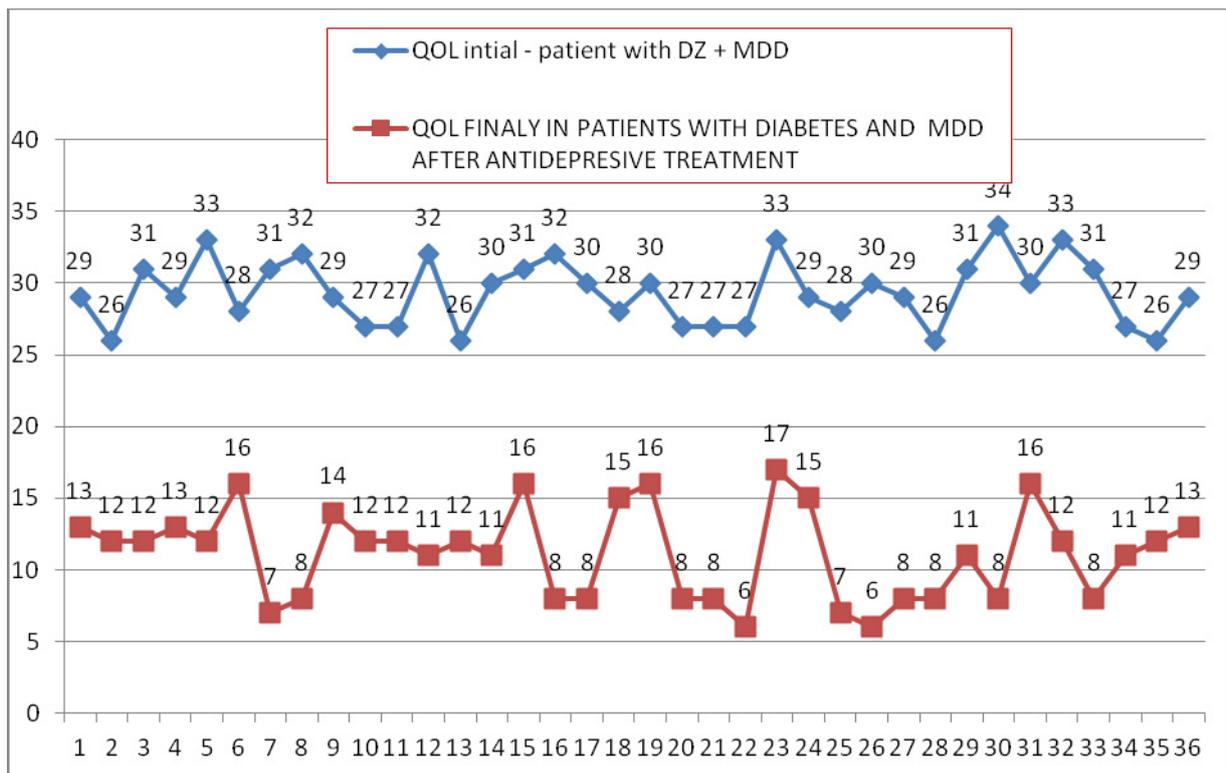


Fig. 6. QOL baseline results and after 6 months – The group of patients with diabetes and depressive disorder

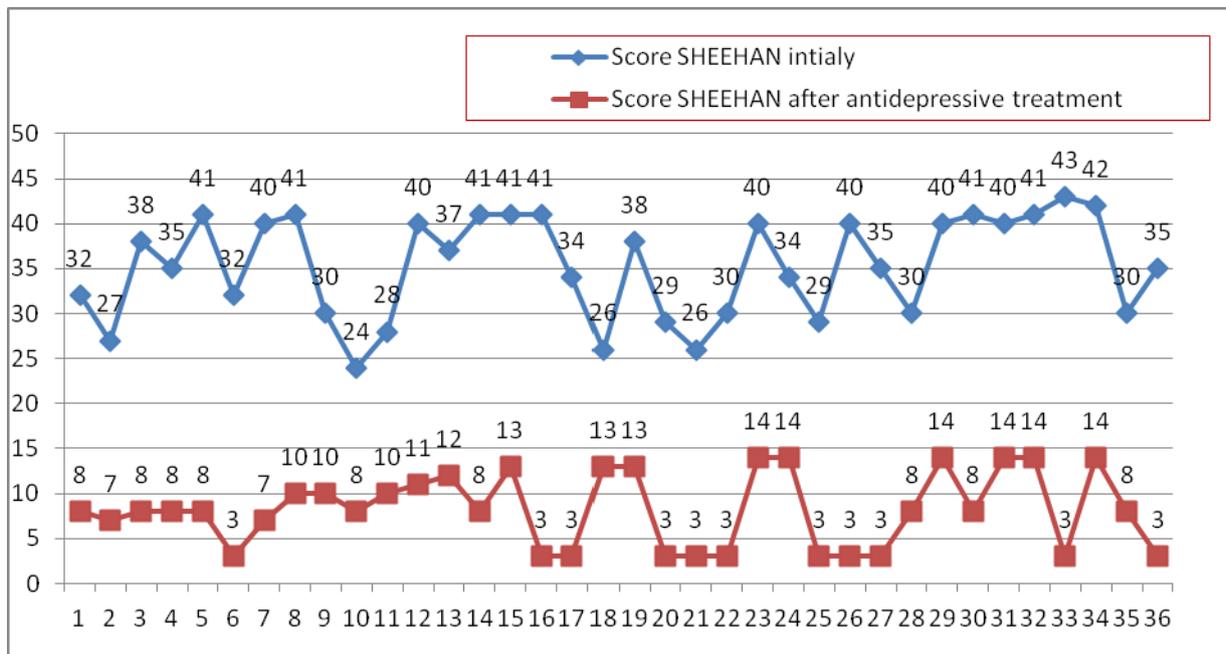


Fig. 7. Sheehan questionnaire baseline results, and after 6 months – The group of patients with diabetes and depressive disorder

The 36 patients with depressive disorder and diabetes mellitus were divided according to antidepressant medication administered as follows: 18 patients receiving Duloxetine 60 mg and 18 receiving SSRIs. We monitored them to see if there was a correlation between the HAMD and QOL scores, both at baseline and at the end of the 6 month period (Table 1, 2, 3, 4). The null hypothesis

(Ho): It is assumed that there is no correlation between the HAMD scores and the quality of life. Negative correlation: low quality of life scores correlate with high Hamilton scores and a higher quality of life (low scores) correlate with low Hamilton scores. In the patients treated with Duloxetine a low quality of life correlated with a high Hamilton score in the initial phase; after 6 months of treatment, the lower depression scores correlated significantly with lower quality of life questionnaire scores, which means that there has been an increase in the quality life (Table 1, 2). In the patients treated with SSRIs, a low quality of life correlated with high Hamilton scores in the initial phase; after 6 months of treatment, although both depression scores and the quality of life questionnaire scores were lower, it was not considered to be statistically significant (Table 3, 4).

Table 1. The correlation between the quality of life and the baseline Hamilton score in patients with Duloxetine

Correlations

		H1D	Q1D
H1D	Pearson Correlation	1	,894**
	Sig. (2-tailed)	,	,000
	N	18	18
Q1D	Pearson Correlation	,894**	1
	Sig. (2-tailed)	,000	,
	N	18	18

** . Correlation is significant at the 0.01 level

Table 2. The correlation between the quality of life and the final Hamilton score in patients with Duloxetine

Correlations

		H3D	Q2D
H3D	Pearson Correlation	1	,521*
	Sig. (2-tailed)	,	,027
	N	18	18
Q2D	Pearson Correlation	,521*	1
	Sig. (2-tailed)	,027	,
	N	18	18

*. Correlation is significant at the 0.05 level (2-tailed).

Table 3. The correlation between the quality of life and the baseline Hamilton score in patients with SSRI

Correlations

		H1S	Q1S
H1S	Pearson Correlation	1	,781**
	Sig. (2-tailed)	,	,000
	N	18	18
Q1S	Pearson Correlation	,781**	1
	Sig. (2-tailed)	,000	,
	N	18	18

** . Correlation is significant at the 0.01 level

Table 4. The correlation between the quality of life and the final Hamilton score in patients with SSRI

Correlations

		H3S	Q2S
H3S	Pearson Correlation	1	,230
	Sig. (2-tailed)	,	,358
	N	18	18
Q2S	Pearson Correlation	,230	1
	Sig. (2-tailed)	,358	,
	N	18	18

Discussion

The studies on patients with depressive disorder also showed a high rate of comorbidity with type 1 or 2 diabetes (12). The results of several studies on patients with diabetes found that depressive disorder in diabetes affected patients is often untreated and incorrectly rated, and that this appears to be a symptom of recurrence (14). The mechanism of the negative impact of depressive disorder on diabetes is considered to be multi-factorial and rather hypothetical.

According to the authors, the comorbidity of the mental disorders in patients with diabetes associates with a negative impact on the quality of life (1, 9) increased costs of care, (11) low response to treatment, (10) poor glycemia control (as evidenced by high levels of HbA1c), (13) increase in the emergency room visits due to diabetic ketoacidosis, (3) increase in the number of hospitalizations, and a higher rate of absenteeism in the workforce, family, social area (7).

Depressive disorders and diabetes relate by bidirectional causality. It has been said that depressive disorders play a causal role in the development of diabetes. A meta-analysis carried out by Mezuk B, et al. showed that people with depressive disorder run a 60% individual risk of developing diabetes mellitus (14). Campayo A, et al. have found a specific association between the depressive disorder of moderate severity, recurrent depressive disorder, untreated depressive disorder and the risk of developing diabetes (5).

Studying the impact of depressive disorder on the quality of life in patients with diabetes in Nigeria, in 2010 Bawo OJ, et al. found that major depressive disorder (MDD) was diagnosed in 30 % of the patients. MDD associated with lower scores on all items of the quality of life questionnaire, WHOQOL - Bref, but without any statistical significance on the items relating to physical health ($p = 0.67$), mental health ($p = 0.59$), environment ($p = 0.70$) or social relationship ($p = 0.58$) (2) .

In a study published in 2004 Goldney et al. showed that the prevalence of depressive disorder in the population with diabetes was 23.6 % compared with 17.1 % among the non-diabetic population. In the case of the patients with diabetes and depressive disorder, the authors noted an increase in each item of the short quality of life form (SF -36) compared to the group of patients with diabetes but no depressive disorder (9). The study we conducted showed that the prevalence of depressive disorder in the diabetic population was 20 %, a percentage that approaches the percentages described in the

literature. These results are in the range of 8.5 to 27.3 % obtained by Gavard et al. (8) in a systematic review of depressive disorder in patients with diabetes.

Several studies have assessed the impact of depressive disorder in patients with diabetes in terms of their functionality or quality of life (4, 6, 8). Brown et al. studied the factors affecting over time the quality of life in patients with diabetes, one of the factors affecting the quality of life in the patients with diabetes being the depressive disorder (4).

The association of depressive disorder with diabetes has a great impact on the quality of life (1). In a placebo-controlled study with Nortriptyline, Lustman demonstrated the benefits of medication in terms of the depressive symptoms, but noted a hyperglycaemic effect on the tricyclic agent (13). In the same study by Lustman et al., Fluoxetine demonstrated a positive impact on the depressive disorder and an improved glycaemia control, although the study was of short duration (13). In our study, the treatment of patients with Duloxetine or SSRI had a beneficial effect on improving life quality reducing the scores on all Sheehan questionnaire items by more than 70 %.

Conclusions

Depressive disorder comorbid to diabetes mellitus associates with a lower quality of life. The coexistence of depressive symptoms and of the basic chronic disease contributes to a lower quality of life, which is why greater attention to identifying and treating these coexisting psychiatric problems is needed, in order to reduce their negative impact on the quality of life. The impact of type 2 diabetes mellitus on the quality of life may be due - in part - to its effect on the development of mental health problems, depressive disorder. The treatment of the depressive disorder is an important link when it comes to improving the quality of life in patients with diabetes. In this context the use of dual antidepressants (Duloxetine) and selective serotonin reuptake inhibitors (SSRIs) appears to be an auspicious pharmacological intervention. The dose of 60 mg of Duloxetine reduced the depressive disorder scores, HAMD depression scores correlated significantly with reduced quality of life questionnaire scores, which translated into an increase in the quality of life. The diabetes doctor must collaborate with the psychiatrist in order to identify all comorbid disorders in patients with diabetes mellitus in order to increase the quality of the services offered to these patients. The quality of the care services provided to the patients with diabetes mellitus can also be expressed by the number of patients undergoing screening for comorbid depressive disorder, and it needs improvement by developing new strategies to tackle it. Both the people involved in the daily clinical management and those involved in establishing the public health policy initiatives aimed at improving the health state of the population with diabetes mellitus must understand which dimensions of the quality of life associate with comorbid depressive disorder in diabetes.

The limitations of this study are as follows: an inability to indicate the causal relation of the depressive disorder decreasing the quality of life, due to the small number of patients; thus the results cannot be generalized to the entire population suffering from type 2 diabetes mellitus.

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THE PLACE OF BURNOUT SYNDROME IN PSYCHIATRY – DISCUSSIONS ON A CASE STUDY

Attila Csorba¹, Otilia Butiu^{2,5}, Mihaela Stoica³, Adriana Mihai^{4,5}

¹Private Psychiatric Ambulatory Odorheiu Secuiesc, Romania

²Neuro –Psychiatric Paediatric Clinic Tg Mures, Romania

³Faculty of Psychology and Educational Sciences, Dimitrie Cantemir University, Tg Mures

⁴University of Medicine and Pharmacy Tg Mures, Romania

⁵IPPD Institute of Psychotherapy and Personal Development, Romania

Abstract

Introduction: The Burnout Syndrome became a reality of today's society, it appears as a response to stress factors and strain of professional life, and it is a more and more frequently used term in psychiatry of the last decade. Despite of fact than in ICD-10 and DSM IV this term is not included; we tried to find its place in psychiatric pathology.

Method: The study was organized in two stages. The first one was to collect and analyze data on this topic from scientific literature for a better understanding and defining of this syndrome. The second stage consisted in a burnout syndrome study case. We tried to find the place of this syndrome in actual psychiatric classification ICD-10 and/or DSM IV.

Results and discussions: The patient admitted in Psychiatric Clinic II Tg Mures presented a symptomatology, which included emotional exhaustion, depersonalisation, deficit of professional satisfaction, relational and motivational deficit, obsessive and ruminative ideas concerning the tensions in professional life. We consider all these symptoms part of burnout syndrome. None of the diagnoses included in ICD-10 and DSM IV had a perfect match with symptomatology of Burnout Syndrome. In the context of this clinical frame we found symptoms, which are specific for other entities like neurasthenia, adjustment disorders or mood disorders (anxious-depressive), which make necessary differential comment.

Conclusions: Keeping in mind the frequency in modern society of this syndrome, we consider opportune question concerning the place of this entity in standard classification of mental disorders.

Key words: burnout syndrome, psychiatric classification, DSM-5, ICD-10.

¹ Correspondence: *Adriana Mihai*, e-mail: dradrianamihai@yahoo.com

Introduction

Although stress is not a new phenomenon, it is continuously gaining a global character and it affects not only every country and socio-professional category, but also the family and society in general.

(1) Burnout Syndrome became an element of our social reality as a response to stress factors and strain of professional life and it is a more and more frequently applied term in the psychiatry of the last decade (2). As a result of some researches, Kahn and his collaborators observed that 5 persons out of 6 are subjected to work tensions, which are sufficiently intense to be suffered by both the individuals in case and by the organization (3).

The idea of this study appeared as the result of the increasing number of patients who solicit psychiatric consults because of the symptoms caused by professional stress.

The experience of other European countries (Switzerland, for example) shows that the Burnout Syndrome is considered to be a medical condition which prevents the ongoing of professional activities and it imposes the necessity of sick leave given for long periods (weeks or months) by the company doctor or the psychiatrist. The more and more widespread occurrence of this syndrome determines the appearance of many professional or community associations which offer psychological counseling and legal support for those suffering from these symptoms.

In this context, our aim has been to find the position of „Burnout syndrome” in the psychiatric pathology. This syndrome is not enlisted in the classification of specific psychiatric diseases DSM IV and ICD-10, therefore, our hypothesis is that the main symptoms of this disease are included in other psychiatric diagnoses.

Material and method

The study was organized in two stages. The first one contains the data collection and analysis of this topic from psychiatric literature with the purpose of understanding and defining this syndrome.

The data collection from the psychiatric literature is based on PubMed data applying terms such as: burnout syndrome- 5827 articles; burnout syndrome and DSM V (8), ICD-10 (8), disease (291), disorders (727), psychiatry (209). 23 articles have been systematically analyzed which strictly referred to the definition and framing of the Burnout syndrome into the actual psychiatric or medical classifications.

The second stage consisted of a burnout syndrome study case hospitalized in the Psychiatric Clinic II, Targu Mures, in February 2009, who fulfilled these criteria and whom we tried to fit to the diagnoses offered by DSM V and/or ICD-10. We have made differential diagnosis with the following entities: depressive affective disorder, neurasthenia, adjustment disorders or mood disorders (anxious-depressive), dysthymia. Through the analysis we have compared the data presented by the patient with the diagnoses from the classifications and from psychiatric literature.

Results and Discussions

The first stage tracked the data collection and analysis from psychiatric literature for a better understanding and definition of this syndrome. We find articles in Pubmed from 1979, and 109 articles with similar preoccupations were already published in 2009 (4,5,6).

A special attention was paid to the definition of this syndrome and to the correlation with the actual medical classifications DSM V and ICD 10.

In the articles analyzed we have found several definitions of this syndrome, some of them being mentioned here:

1. Physical and emotional responses which appear when the requirements of the job do not correspond to the abilities and resources of the person, causing health deterioration (7).
2. An emotional, cognitive, behavioral, physiological reaction to the aggressive and harmful aspects of work, to the circumstances of work and to the organizational atmosphere. It is a state characterized by high levels of distress and by the feeling of being unable to fulfill the required tasks (8).
3. It represents the reaction of the individual exposed to an excessive pressure or other various requests from his/her environment (9).
4. A state of physical, emotional and mental distress caused by a long implication of the individual in emotionally strenuous situations (10). It is described as a slowly developing process without symptoms, which leads to emotional exhaustion and social withdrawal.
5. A “chronic disease” characterized by physical and emotional exhaustion and often generated by constant frustration at work (12).
6. A delimitation and definition of the Burnout syndrome was made by Maslach and Jackson in 1986, often cited by several authors.

They describe the burnout syndrome as a “syndrome that has 3 dimensions”:

- a. Depersonalization – the person distances him/herself from the world, which he/she begins to see impersonally;
- b. The reduction of personal realization;
- c. Emotional exhaustion- the person feels emptied of personal emotional resources and becomes highly vulnerable to stress-factors (13).

Thus, the most common symptoms of this syndrome can be:

- Physical symptoms: fatigue, frequent headaches, gastrointestinal disorder, insomnia, the change of eating habits, the use of psychotropic medicine;
- Psychological manifestation: feelings of guilt, of negativism, mood disorders, irritability, low empathy and self-confidence, reduced capacity of response;

- Behavioral reactions: frequent absences or delays, the negation of communication, the tendency to avoid telephonic contacts and to call off appointments, the use of standardized procedures, the depersonalization of relations.

The work of Maslach et al. focuses on the health of physicians, nurses and psychiatrists.

The results show three phenomena: the manifestation of emotional exhaustion, the development of negative feelings and perceptions towards their patients and professional skills crisis (13).

7. According to World Health Organization, organizational stress is a state perceived as negative by the employee, accompanied by discomfort or physical, mental and/or social malfunctions, a state which appears as the result of the demands and expectations to which the person is exposed to in his job and which he/she is unable to respond to. Among the symptoms we mention: a distinguishable change in performance, the loss of motivation, uncertainty, the incapacity to make decisions, the decrease of the power of concentration.

The symptoms include physical, psychological and behavioral aspects:

- The increase of coffee, alcohol and even drug intake;
- Depression, low self-respect, pessimism, social seclusion;
- The increase of absenteeism and late comings;
- Fatigue, irritability, muscle tension, gastrointestinal affections;
- The loss of the sense of humor and the emphasis of guilt.

As we remarked all these definitions share the existence of some overloaded professional condition and the description of the consequences of professional stress on the person on a psychological, physical and behavioral level.

Attempting to include these symptoms into a syndrome which already exists among the psychiatric diseases, we can observe that there is no disease which would suit the descriptions above (Table 1). We have compared the Burnout syndrome to depressive affective disorder, neurasthenia, adjustment and anxious-depressive disorder. The most common points have been established with the anxious-depressive disorder.

Table 1. Differential diagnosis of other psychiatric entities

Symptoms	BURNOUT	Depression	Neurasthenia	Adjustment disorder	Dysthymia	TAD
Depersonalization	+	-	-	-	-	-
Sleep disorders	+	+	-	+/-	+	+
Decrease of efficiency at work	+	+	+	+	+	+
Emotional exhaustion	+	-/+	-	-	-	-
Irritability	+	-/+	-	+/-	-	+
Anxiety	+	-/+	-	+/-	-	+
Feeling of emptiness	+	-	-	-	-	+

Symptoms	BURNOUT	Depression	Neurasthenia	Adjustment disorder	Dysthymia	TAD
Preoccupation for the job	+	-	-	-	-	-
Social seclusion	+	+	+	+	-	+
Cynicism	+	-	-	-	-	-
Fatigue	+	+/-	+	+/-	+	+
Depressive disposition	+	+	-	+	+	+
Feeling of guilt	+	-/+	-	-	-	-
Low empathy	+	+	-	-	-	-
Low self-confidence	+	+	+/-	+	+	+
Absences from work	+	-/+	+/-	+/-	-	+/-
Digestive disorders	+	-/+	+	+/-	+	-
Lack of dialogue	+	-/+	+/-	+/-	-	+/-

Case study

S. A. male patient of 30 years old from the urban environment is hospitalized because of severe insomnia (he sleeps 2-3 hours/ night), anxiety and depressive symptoms of average intensity. He lives with his parents, has 3 sisters, second place in brotherhood. His father is a chronic alcoholic, aggressive in his childhood (conflicts with mother, neighbors). The patient is not married but he had some few-month-long relationships. He broke up with his girlfriend a month before his hospitalization. The network of social support is inadequate, in terms of quality and quantity. A month before his hospitalization he suffered a minor cranio-cerebral trauma (motorbike accident). As far as his educational and professional development is concerned, the patient has graduated 12 grades with good results; he has worked at the community police station for 7 years then at a Romanian-German company. He denies the consumption of toxics. He is a person with few friends but active on a professional level. At the SCID II personality test he showed obsessive compulsive personality traits.

Case history: 30 - year-old patient with multiple psycho traumatic episodes (motorcycle accident, changing jobs, working more than 10 hours/day without holidays for 2 years, modification of the management team, breaking up with his girlfriend because of stress), displays a psychopathological state a month before his hospitalization dominated by insomnia (2-3 hours a day), mentism, anxiety, rumination on job and home problems, logorrhea, panic attacks, palpitations, tremor, psychomotor agitation. The examination of the physical state reveals expressive, anxious facies, appropriated clothing, cooperative attitude, temporo- spatial, auto- and allo-psyche orientation, headaches, excessive attention to predominant themes, hypermnesia to these themes, accelerated rhythm of thinking, mentism, ruminations, anxiety, panic attacks, hypobulia interchanging with hyperbulia, severe insomnia, and personality with obsessive-compulsive features. He was diagnosed with

persistent depressive-anxious episode. In Table 2, we have made a comparison between the symptoms of the patient and the symptoms of the Burnout Syndrome.

Table 2. Comparison of the patient's symptoms with the symptoms of Burnout Syndrome

Symptoms	BURNOUT	Patient's symptoms
Depersonalisation	+	+
Sleeping disorders	+	+
Decrease of performance	+	+
Emotional exhaustion	+	+
Irritability	+	-
Anxiety	+	+
Sense of emptiness	+	+
Preoccupation for work	+	+
Social withdrawal	+	+
Cynicism	+	-
Fatigue	+	+
Depressive mood	+	+
Sense of guilt	+	-
Low empathy	+	+
Low self esteem	+	+
Absences from work	+	-
Digestive disorders	+	-
Lack of communication	+	+

Conclusions

No diagnosis offered by DSM IV and ICD-10 does entirely correspond to this syndrome. In the above mentioned context the clinical features include symptoms characteristic to other entities such as neurasthenia, anxious-depressive disorder, which generate comments. Most of the common characteristics are to be found with the anxious-depressive disorder. Taking into account the frequency of this syndrome in modern society, we consider the opportunity of including this entity in the standard terminology and classification of mental disorders

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AN EXPERIMENTAL MODEL OF ISCHEMIA-INDUCED CHANGES INTO THE GLYMPHATIC SYSTEM OF THE BRAIN

Dragos Marinescu¹, Laurentiu Mogoanta², Adonis Sfera³,
Roberto Gradini⁴, Carolina Osorio⁵, Adrian Preda⁶

¹University of Medicine and Pharmacy of Craiova, Psychiatry Discipline

²University of Medicine and Pharmacy of Craiova, Histopathology Discipline

³Department of State Hospitals, Patton State Hospital

⁴Sapienza University School of Medicine, Rome

⁵Kaiser Permanente Southern California

⁶University of California Irvine School of Medicine.

Abstract

Introduction: The brain neurovascular unit (NVU) is situated at the interface between information processing and energy supply. The glymphatic draining system operates within the matrix of the NVU, circulating the brain interstitial fluid (ISF), clearing it from molecular waste. This system facilitates the exchange between CSF and ISF via the aquaporin 4 (AQP 4) water receptors found in astrocytic end-feet opposed to brain microvessels. We hypothesize that acute or chronic ischemia results in impairment of the glymphatic system by decoupling pericytes from the basal membrane and astrocyte end-feet from the endothelial cells of brain microvasculature with accumulation of molecular debris and protein aggregates, ultimately triggering neuronal apoptosis. In order to test this hypothesis we created a rat model of ischemia-induced dysfunction of the of the glymphatic system in the nucleus basalis of Meynert and the hippocampus.

Method: Our study used 15 Wistar rats divided in three groups of five each. Clipping of left, right and bilateral internal carotid artery was accomplished surgically in each group. After 7 days, standard histological preparations were obtained of the ventral hippocampus and the Nucleus Basalis of Meynert.

Results: The following events were identified leading to neuronal apoptosis: breakdown of the NVU with loss of endothelial cells-astrocyte coupling, microvessels edema with fragmentation of astrocytic end feet, suggestive of glymphatic system disruption, loss of apposition of astrocytic end feet and brain microvasculature.

Discussion: Ischemia leads to pericyte dysfunction with detachment of astrocytic end-feet from the endothelial cells. Since astrocytic end feet are rich in APO 4 receptors, we suggest that disruption of these structures impair glymphatic circulation, leading to accumulation of protein aggregates and waste, opening a vicious circle in which inadequate clearance leads to accumulation of waste, neuronal apoptosis, which leads to additional debris and further apoptosis. Disruption of glymphatic pump in the nucleus basalis of Meynert and the hippocampus may explain impairments in cognitive domain in neuropsychiatric disorders as being caused by accumulation of molecular debris or protein aggregation due to failure of local clearance.

¹ Correspondence: Adonis Sfera, e-mail: adonis.sfera@psh.dsh.ca.gov.

Conclusion: Disruption of the glymphatic system in the hippocampus and/or nucleus basalis of Meynert with failure to clear inflammatory by-products, autoantibodies or protein aggregates may explain impairments in the cognitive domain of schizophrenia and other neuropsychiatric disorders. Pathological changes revealed by our model are consistent with those described by Hanson and Gottesman in schizophrenia and N. Rouach in inflammation, epilepsy and ischemia.

Key words: *neurovascular unit, brain interstitial fluid, aquaporin 4.*

Introduction

The concept of the neurovascular unit (NVU) arose from coupling in the central nervous system between the neuronal activity and the local blood flow. Over time this concept evolved to signify an integrated system of neuronal, non-neuronal cells, and interstitial matrix working together at the interface between information processing and energy flow (Iadecola, 2004).

The NVU has received limited attention in neuropsychiatry, but this state of affairs is beginning to change, especially since the discovery of the glymphatic system which operates within the NVU matrix as a sort of molecular pump that facilitates the exchange between the ISF and CSF via paracapillary spaces (Iadecola, 2004). The glymphatic system consists of an anatomic pathway whose function originates with CSF descent into the NVU matrix via paraarterial spaces, pushing the ISF (carrying molecular waste) towards the paravenous space and out of the NVU matrix. Pericyte contractility was suggested as the originator of pressure gradient necessary for this exchange (Nedergaard, 2012). The glymphatic pathway utilizes AQP 4 water receptors in astrocytic end-feet for drainage, thus the integrity of these receptors is crucial for the proper functioning of the system (Gundersen, 2013).

The physiological function of the glymphatic system is drainage and clearance of protein aggregates such as beta amyloid, and other molecular waste. The malfunctioning of the glymphatic pump in the nucleus basalis of Meynert and/or the hippocampus may be involved in the etiology of cognitive deficits in some neuropsychiatric disorders, such as schizophrenia. Development of animal models of glymphatic pathology would help study two kinds of pathological changes:

1. Local changes produced by accumulation of molecular waste or aggregates in the NVU matrix, and
2. At-a-distance (diaschisis-type changes) caused by disruption in cellular communication by volume transmission.

The functions of the glymphatic system and its pathology has propelled the NVU to the status of a structural and functional unit of the brain along the lines of the lung's alveolus or the kidney's nephron (Xue, 2013).

In spite of the importance of the NVU and the glymphatic system for neuropsychiatric disorders, as of now, there is a paucity of animal models for studying this pathology. The purpose of our study is to provide such a model that would allow us to understand and study the role of the CSF-ISF exchange within the NVU, along with its pathology.

Method

Our study used 15 Wistar rats divided in three groups of five each. Clipping of left, right and bilateral internal carotid artery was accomplished surgically in each group. The animals were sacrificed after 7 days and standard histological preparations were obtained of the ventral hippocampus and the Nucleus Basalis of Meynert. All slides were stained using hematoxylin and eosin, hematoxylin, periodic-acid schiff (PAS) stain, immunohistochemical endothelial markers CD34, anti-gliial fibrillary acidic protein antibody (GFAP). The images were obtained by optic microscopy magnification x100 and x200.

Results

The following events were identified leading to neuronal apoptosis: breakdown of the NVU with loss of endothelial cells-astrocyte coupling, microvessels edema with fragmentation of astrocytic end feet, suggestive of glymphatic system disruption, loss of apposition of astrocytic end feet and brain microvasculature.

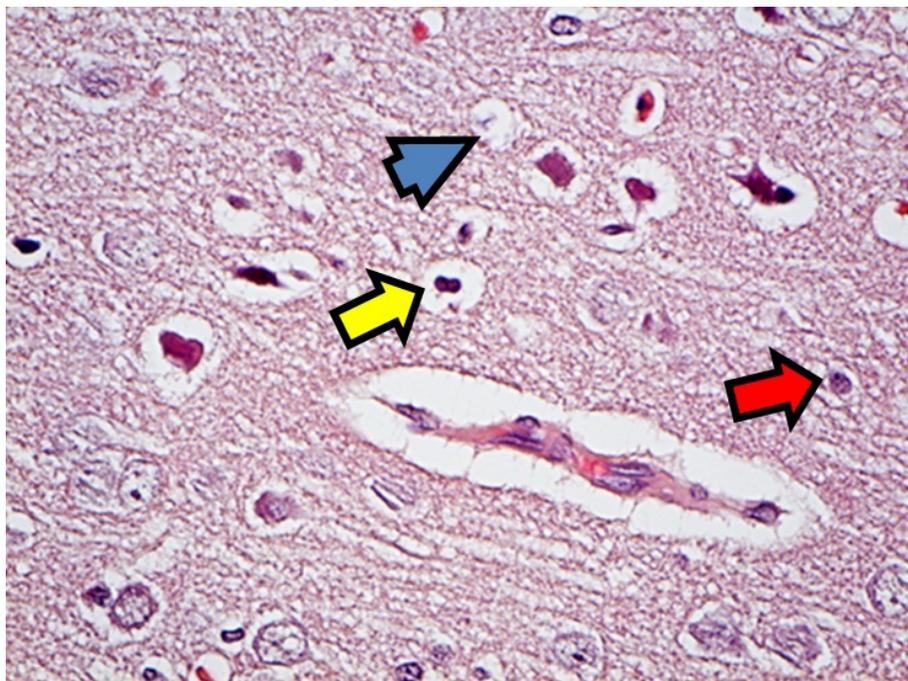


Fig. 1. In the central area a collapsed capillary is seen surrounded by pericapillary edema and fragmentation of astrocytic end feet. Accumulation of molecular debris from disintegration of astrocytic end-feet containing AQP 4 water receptors. Surrounding the capillary there are neurons in different stages of apoptosis. Apoptotic neuron (blue arrow), partially apoptotic neuron (yellow arrow), healthy neuron (red arrow). Hematoxylin and eosin staining, magnification x 200.



Fig. 2. Perivascular edema with neuronal and dendritic fragmentation causing molecular debris that cannot be cleared by the glymphatic system. PAS hematoxylin staining, magnification x200.

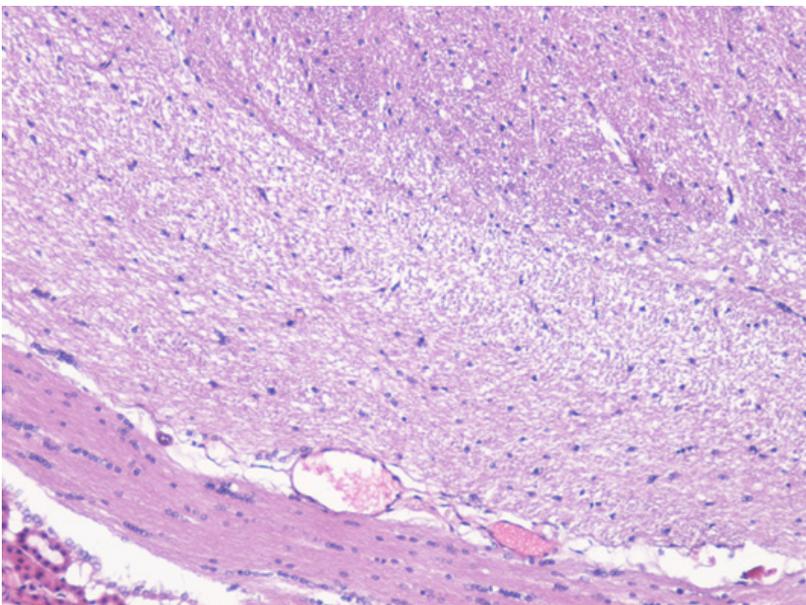


Fig. 3. Nucleus basalis of Meynert: changes in capillary structures with pericapillary edema and various stages of apoptosis of the cholinergic interneurons. Glymphatic system failure leads to accumulation of molecular waste resulting from neuronal disintegration leading to a vicious circle of further apoptosis. Hematoxylin and eosin staining, magnification x100.

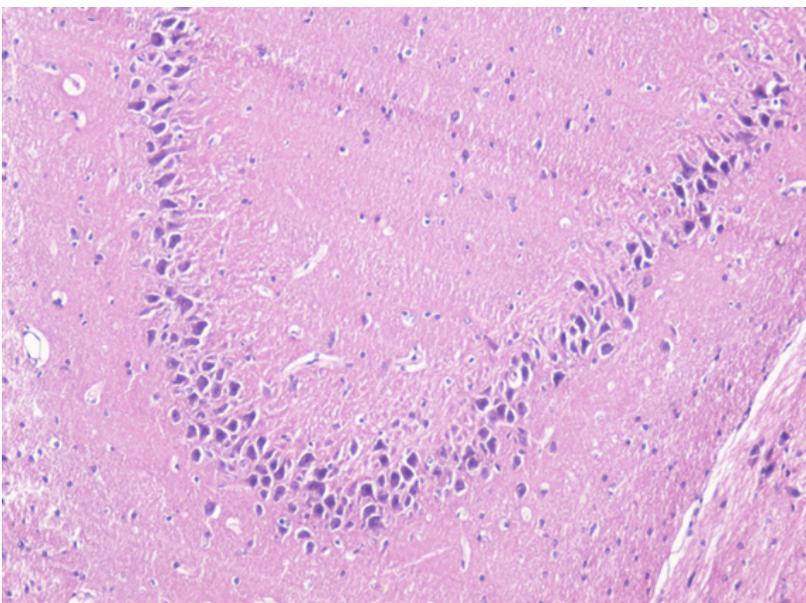


Fig. 4. Ventral hippocampus: neuronal apoptotic changes can be observed resulting in build-up of molecular waste that cannot be cleared by the glymphatic system.

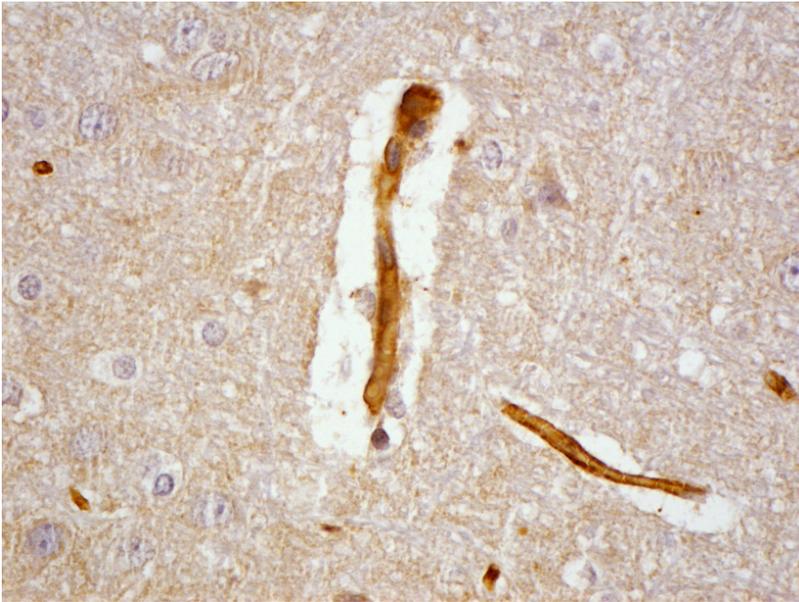


Fig. 5. Profound anatomic changes of the NVU with pericyte detachment from endothelial cells and astrocyte damage with accumulation of protein aggregates such as glial fibrillary acidic protein that cannot be cleared by the glymphatic system due to AQP 4 receptors loss. Endothelial specific CD 3 staining anti-glial fibrillary acidic protein antibody (GFAP), magnification x200

Discussion

The glymphatic system operating within the NVU opens new vistas into psychopathology research. The role of the glymphatic system in sleep is well documented along with sleep related clearance of beta amyloid (Xie, 2013). Recent studies demonstrate that sleep brain circuits overlap with circuits involved in major neuropsychiatric syndromes such as schizophrenia or bipolar disorder (Foster, 2013), bringing the NVU and the glymphatic system in the center stage of psychopathology.

Inefficient or delayed clearance of molecular waste such as beta amyloid, apoptosis by-products, inflammatory or autoimmune by-products may produce local changes and pathology. For example, neuromyelitis optica (NMO) is an autoimmune disorder with psychiatric manifestation whose etiology involves autoantibodies to AQP 4 receptors in astrocytic end-feet, delaying ISF clearance (Jarius, 2013). Delayed and inefficient beta amyloid clearance was demonstrated in transgenic mice bred without AQP 4 receptors (Iliff, 2012).

Protein aggregation is the hallmark of degenerative disorders, such as Alzheimer's disease (beta amyloid), Parkinson's disease (alpha synuclein), Huntington's disease (polyglutamine) among others. Protein aggregation is believed to be the result of dysfunctional proteostasis such as failure of clearance of misfolded proteins. Disrupted-in-schizophrenia 1 (DISC 1) gene with linkage to chronic psychosis was found to produce insoluble aggregates in the brain ISF (Bader, 2012). Failure of the glymphatic system to clear these aggregates may lead to pathology caused by accumulation as demonstrated by Bader who identified collapsing-response mediator protein 1 (CRIMP 1) in a large Finnish cohort of patients with chronic mental illness (Bader, 2012).

Furthermore, the view that inefficient glymphatic clearance (possibly due to inflammation and block of AQP 4 receptors) was also suggested by a recent large scale epidemiological study in psychiatry (Bechter, 2010) demonstrating that autoimmune disorders acquired during lifetime significantly and additively increased the risk of psychoses.

A properly functioning glymphatic system ought to be able to clear residues such as autoantibodies or inflammatory by-products. Mild encephalitis with low level neuroinflammation and autoimmunity (propagated via CSF) was suggested in schizophrenia and other psychoses (Bechter, 2013). Evidence for autoimmunity to NMDA receptors (Zandi, 2011) lends further support to the clearance hypothesis and may imply new treatment approaches (Lennox, 2012).

CSF examination in neuropsychiatric disorders looking for molecular waste accumulation may help develop novel biological markers and improve the presently limited treatments, especially in treatment-resistant schizophrenias.

Another area of interest is at-a-distance pathology induced by faulty molecular signaling via volume transmission.

The function of neuronal networks is dependent on precise ISF concentrations of ions, neurotransmitters, neuropeptides, growth factors, neurohormones, nucleosides, and vitamins. The glymphatic system may be crucial for maintaining adequate concentrations of these substances, and thus for homeostasis. In addition the glymphatic system uses the same long distance pathways as volume transmission, namely the paravascular channels, thus becoming a communication platform in the brain, a sort of wireless connectome with implications in the long distance signaling via the CSF (Hartung, 2012). The connectome role of the glymphatic system becomes evident in the influence the ICF-CSF composition has on the brain parenchyma. For example, during early development, disturbed CSF composition can induce pathological conditions in the brain parenchyma in experimental animals. In preclinical studies impaired development of cortical neurons was induced in vitro by adding CSF from hydrocephalic rats to cortical precursor cells obtained from normal rats (Owen-Lynch, 2003).

The importance of at-a-distance CSF and ISF signaling was demonstrated by experiments involving the transfer of CSF from sleep-deprived goats into normal rats. CSF-transplanted rats exhibited fatigue, indicating that CSF signals were transferred and that they influenced brain activity (Hartung, 2012). Another experiment involved ablation of SCN in hamsters. As expected, this procedure was followed by disturbed circadian rhythm. Next, suprachiasmatic nucleus (SCN) tissue encapsulated in a semipermeable polymeric membrane (that prevented synapse formation) was transplanted in SCN-ablated hamsters. Following transplantation the circadian rhythm was restored in these animals. This results prove that cellular communications occur at a distance via ISF and CSF exchange in the glymphatic system (Silver, 1996). Poorly understood at-a-distance neurological phenomena such as diaschisis may be explained in this manner.

Our research demonstrates that ischemia leads to pericyte dysfunction with detachment of astrocytic end-feet from the endothelial cells. Since astrocytic end feet are rich in APO 4 receptors, we suggest that disruption of these structures impair glymphatic circulation, leading to accumulation of protein

aggregates and waste, opening a vicious circle in which inadequate clearance leads to accumulation of waste, neuronal apoptosis, which leads to additional debris and further apoptosis. Furthermore the ISF-CSF exchange may be impaired as a result of pericyte pump failure to maintain adequate pressure gradient for glymphatic circulation. Recent data demonstrated that pericytes produce the neuroprotective apolipoprotein E (ApoE) which modulates A β cytotoxicity and A β removal near brain microvessels (Bruinsma, 2010, Sagare, 2013).

Disruption of glymphatic pump in the nucleus basalis of Meynert and the hippocampus may explain impairments in cognitive domain in neuropsychiatric disorders as being caused by accumulation of molecular debris or protein aggregation due to failure of local clearance. Our group is currently working on a pathogenetic model of at-a-distance, diaschisis -like changes, in areas of the brain not connected to the site of original injury.

Study Limitations: Our study is to be considered a preliminary project designed mostly to raise questions and give directions for future endeavors. For example, the study could be improved by neuroimaging of the glymphatic system via contrast-enhanced MRI or mRNA quantitative analysis of AQP 4 water receptors that could be accomplished by techniques such as RNase protection assay. A control group could offer more balance by demonstrating that NVU changes were, indeed the result of ischemia.

Conclusions

NVU is situated at the cross roads of information processing and metabolism. It consists of neuronal, non-neuronal cells and an ISF matrix. This busy space contains signaling molecules, and protein aggregates from the combustion chamber of the synapse. The glymphatic system in the NVU matrix operates as a molecular pump, facilitating ISF-CSF exchange along with molecular waste produced by neuronal and glial activity. In addition, by virtue of utilizing the same long distance pathways as volume transmission, the glymphatic system becomes a novel communication platform in the brain.

The rat model in our study offers a working hypothesis marked by a cascade of successive events: ischemia leads to damage of astrocytic end-feet, disruption of the glymphatic system, accumulation of molecular waste, neuronal apoptosis, failure of information processing.

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COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

Mihai Mutica¹, Ileana Marinescu², Mihail Pirlog²

¹Doctoral School, U.M.Ph. Craiova, "Elisabeta Doamna" Psychiatry Hospital, Galati, Romania

²University of Medicine and Pharmacy of Craiova, Romania

Abstract

Individuals with schizophrenia present altered cognitive functions whose intensity varies depending on the neurobiological mechanisms involved in schizophrenia. There are few studies regarding the evolution of cognitive impairment in patients with schizophrenia and prolonged course, who at the time of the assessment exceeded 65 years of age. The quantification of cognitive impairment is not fully clarified related to the disease and to the occurrence of positive psychotic symptoms. Cognitive impairment is reported during the prodromal period, the first episode and the subsequent development of the disease, remaining relatively stable or worsening after the first psychotic episode. The cognitive impairment is aggravated by the persistence of the negative symptoms and EPS symptoms, independent or induced by the antipsychotic medication (cortical-subcortical disconnectivity).

Regarding the etiopathogenic mechanisms, the cognitive impairment sustains the neurodevelopment theory, the dopamine deficit and the alteration of frontal and hippocampal cerebral structures. Cognitive impairment includes a set disorders regarding attention, working memory with decreased information processing, alteration of executive functions, learning and memory deficits, decreased expressive and receptive language skills, impaired visual perceptive skills, social cognition deficits (predominantly facial emotional expressions and prosodical). Cognitive impairment remains the most important prediction factor of functional independence in patients with schizophrenia, especially for older patients. For elderly patients with schizophrenia the cerebral vascular factor has a great importance.

Key words: *cortical-subcortical disconnectivity, vascular factor, alteration of frontal and hippocampal cerebral structures.*

Schizophrenia is a major psychiatric disorder with multiple factorial etiology, polymorphic clinical presentation and generally chronic and severe evolution. The current concept of the disease reassesses the presence and the importance of cognitive deficit in schizophrenia. If in the past it is believed that cognitive impairment is a marginal element or strictly a result of medication, it is now accepted that cognitive impairment is central to explanations regarding the etiopathogenesis of the disease, clinical and functional consequences.

The purpose of the paper is to present the latest trends in the literature on cognitive deficit, to systematize the relationship between biological, clinical and functionality in schizophrenia, to

¹ Correspondence: Mihai Mutica, e-mail: mutica1@yahoo.com.

presenting the data in our own research. The paper will discuss the importance of cognitive deficit, its involvement in the etiopathogenesis of schizophrenia (especially in terms of disconnectivity); it will present systematic neuropsychological domains investigated in the literature and will examine aspects of the disease, involvement of vascular, controversies and current trends.

Presence, extent and severity of cognitive impairment are generally not contested (Bonner-Jackson, 2010). Current data show the presence (Censits, 1997) of the cognitive deficit in prodromal period (since childhood), during the first episode of psychosis (Saykin, 1994, Bilder, 2000) and lifetime (Kurtz, 2005, de Gracia Dominguez, 2009).

Cognitive impairment is present in prodromal period of other major psychotic disorders, but is specifically associated with schizophrenia. Cognitive interests more aspects of cognitive functioning. Investigated neuropsychological domains primarily aimed at information processing speed; efficient and rapid assimilation of information is decreased (Kalkstein, 2010). In relation to information processing speed, attention is impaired and, rather than simple attention, working memory is impaired and also the allocation of attention to relevant objects (involving executive functions); the ability to sustain attention (vigilance) is decreased, as well (Fuller, 2006).

In terms of memory, working memory is impaired and also visual and verbal memory (but more verbal than visual). Evocation (recognition memory) is affected, with the particularity that there is a deficit in recalling visual information rather than the verbal. Overall, in schizophrenia there is memory impairment rather than evoking impairment (Kalkstein, 2010).

Language impairment is evidenced by studies that testify significant difficulties in expressive and receptive language area (Fuller, 2006), notably the difference between the semantic and phonemic fluency: semantic fluency (in relation to personal experience) is more impaired than phonemic fluency (based on connections between letters) (Dickinson, 2007). Executive functions are related to the prefrontal cortex and include a wide range of features of the psyche - will, consciousness, planning, abstraction, flexibility / adaptability thinking, initiating and sustaining an action. Subjects with schizophrenia have affected cognitive processes related to the field of executive functions and their study was focused on Wisconsin Card Sorting Test (involving abstraction, inadequate response inhibition, cognitive adaptation strategies in relation to environmental changes), Stroop Test (involving selective attention and usual response inhibition), Trail Making test B (in which the subject alternates between numbers and letters, it assesses executive functioning), Controlled Oral Word Association test (COWAT; a verbal fluency test) (Fuller, 2006).

Social cognition is a relatively new but whose importance is recognized by adding it to the MATRICS battery and involves process of collecting and interpreting information about members of the species. Social cognition includes emotional processing, social perception, social knowledge, theory of mind, attributional bias (Green, 2008). These subdomains are important in assessing the

functionality of subjects with schizophrenia (Couture, 2006). In the first place, there were studies about emotion perception through recognition of facial affect and emotional prosody recognition (Kohler, 2003; Hoekert, 2007), both affected in subjects with schizophrenia compared to the general population and from groups of other psychiatric disorders. In patients with schizophrenia is affected also the expression of emotions, both at facial (Kring, 2008) and the verbal level (Couture, 2006) and these impairments are also noticeable compared with the general population or subjects with other psychiatric disorders or neurological disorders. On the other hand, the deficit in processing emotions is due to inappropriate emotional expression rather than emotional experience per se (which is conserved) (Hoekert, 2007).

Theory of mind aims ability to draw general conclusions from particular elements and to make representations on the mental states of others. Erroneous assumptions about the thoughts and feelings of others lead to exacerbation of psychosis (Penn, 2008).

Besides the above, in schizophrenia are decreased visual perceptual skills and the constructional and fine motor skills (Kalkstein, 2010). In addition to these impairments on particular areas, subjects with schizophrenia have a global deficit in terms of general intellectual functioning. There are discussions in literature whether or not the overall deficit comes from summing impaired in these areas; it seems that one can speak of a global cognitive impairment with specific areas affected in varying degrees (Dickinson, 2008).

Neuropsychological deficits delineate a vulnerable endophenotype describing both people with schizophrenia and unaffected relatives. This vulnerable endophenotype met in healthy relatives of those with schizophrenia encompasses difficulty paying attention, impairment of verbal memory and executive functions (Snitz, 2006).

Overall, the substrate of the deficit would be in lowering gray matter, white matter density loss, poor integration of neural signals (Penn, 2008).

There is a consensus today that, in terms of neuropathological features of schizophrenia, there is reduced neuronal density increase and decrease cortical dendritic tree (Andreasen, 2010).

Biological changes come from a genetic vulnerability present in childhood (formation and neuronal migration, cortical lamina formation) and become apparent at the onset of schizophrenia, continuing in various proportions throughout life (synaptic plasticity) and gathering themselves with others that are specific to adult (i.e. ageing) (Snitz, 2006). In this way, the dichotomy between neurodevelopmental and neurodegenerative model is reconciled by the concept of neuroprogression (Andreasen, 2010). Structural abnormalities in schizophrenia occur practically in any cortical or subcortical structures. Magnetic resonance imaging (MRI) studies indicate impaired cavum septi pellucidi, lateral ventricles, amygdala and hippocampus, third ventricle, basal ganglia, superior temporal gyrus, corpus callosum, temporal lobe, frontal lobe, parietal and occipital lobes, thalamus,

cerebellum, cerebral global volume (Shenton, 2001). The combination of structural abnormalities with poor performance in neuropsychological domains highlights the following: 1) enlarging ventricle III as against global brain size is associated with deficit in abstraction, flexibility of thought, language, attention; 2) enlargement of the lateral ventricles is associated with decreased psychomotor speed and attention only in women with schizophrenia; 3) prefrontal archicortex size is associated with executive functions in both sexes, regardless of diagnosis; 4) temporal lobe, hippocampus, gyrus parahippocampal - speed and accuracy of cognitive function, memory, executive functions, thesaurus, abstraction function; 5) size of striatum is related to goal-oriented behavior (but not persevering) in schizophrenia; 6) enlargement of the cerebellum is associated with increased IQ in the normal population and in women with schizophrenia; 7) increasing the size of white vermis is associated with verbal disorders in patients with schizophrenia. (Antonova, 2004)

If at the psychotic onset of schizophrenia is obviously a cognitive deficit, the question is what happens after the initial psychotic period. Some studies show that global intellectual deficit is not emphasized (Gold, 1999; Hoff, 1999), while others highlight the significant decline from premorbid intellectual ability (Sheitman, 2000) and continued decline in geriatric age (without falling into the pattern of dementia) (Harvey, 1999). A 20-year study of patients with schizophrenia (compared with those with other psychiatric disorders, both psychotic and non-psychotic) shows significant cognitive decline in the first years after onset in the area of processing speed of accessing information and general knowledge; after then, this deficit relatively flattens (compared with those of other diagnostic groups) (Bonner-Jackson, 2010). The absence of a rapid decline in older patients with schizophrenia who are maintained in the community is shown in the literature (Zorilla, 2000); by contrast, chronic schizophrenic institutionalized subjects shows an obvious cognitive decline, but different in the areas affected by Alzheimer (Hoff, 1999, Davidson, 1996). The pattern of cognitive decline in elderly schizophrenia subjects remains different from Alzheimer's, yet some data show a slight deterioration after 65 years in schizophrenic patients (Friedman, 2001).

Cognitive deficit is thus in relation to the precipitation of psychotic symptoms (Weickert, 2000), remains relatively stable throughout evolution, it is global (verbal area, attention and memory being more affected), it persists after remission of psychotic symptoms and it is in relationship but separated from negative symptoms (Harvey, 1996).

From the historical point of view, several models have been proposed. Prefrontal cortex was the first targeted ever since Kraepelin and after then the cortical structures that are in relationship with prefrontal cortex were questioned. It is discussed thus the model of disconnectivity in cortico-cerebellar-thalamo-cortical circuitry, model that explains the cognitive and motor disorders, based on the arguments of Andreasen (Andreasen, 1998) on cognitive dysmetria in schizophrenia; this dysmetria leads to deficiency in processing, prioritization, restoration, coordination and response

information. The studies were based on brain imaging, brain imaging (fMRI - functional magnetic resonance imaging, diffusion tensor imaging - DTI, MTR – that is DTI plus magnetic transfer imaging), electroencephalography (EEG), magnetoencephalography.

If initially it was considered that only hypofunction is particular for prefrontal cortex in patients with schizophrenia (Carter, 1998), subsequently it was revealed prefrontal hyperactivity (Manoach, 2003), both being present in variable proportions and without a clear ratio in schizophrenia. Both hypo and hyperfunction may be ineffective neural processing or modular compensation. In terms of dopaminergic transmission, increased dopaminergic transmission in the striatum (characteristic of schizophrenia) and the D2 frontal receptor binding potential (Abi-Dargham, 1998) are involved in the positive symptoms of schizophrenia (plus aberrant reward processing) (Kapur, 2003), while D1 and D2 prefrontal receptor imbalance are related to positive and negative symptoms (Seamans, 2004). Negative symptoms are attributable to the link between prefrontal and amygdala, fronto-amygdala circuitry being dysfunctional in patients with schizophrenia and their relatives (Hoptman, 2010, Tian, 2011).

The topic of the dysfunction of a certain region was subsequently replaced by models on connectivity (Schmitt, 2011). Disconnectivity targets interactions between brain regions and involves a neurodevelopmental path (Stephan, 2009). Genetic polymorphisms characteristic of schizophrenia vulnerability leads to disruption of axonal growth, synaptic plasticity and architecture (Arguello, 2012), in relation to prefrontal receptor hypofunction of N-methyl-D-aspartate (NMDA) which inducing overstimulation of D2 receptors in striatum which in turns will weaken cortical glutamate transmission, via striatal interneurons in charge of the gamma-aminobutyric acid (GABA) (Howes, 2009; Laruelle, 2005).

Disruption connectivity is conceptualized in terms of a (dis)functional network dynamics. This means disconnectivity model should be viewed primarily as a disruption of information between brain regions and only in the background will appear references to structures involved, ways of communication or causation. Effective connectivity describes the flow of information in a network of brain structures and is studied (described) by statistical methods such as psychophysiological interactions, structural equation modeling, dynamic causal modeling and Granger Causality (Nejad, 2012).

Nonlinear mathematics is used in brain connectivity study, quantifying brain networks; the graph describes a network from a mathematical perspective. Regular networks are characterized by short paths and high connectivity with neighbors (high clustering, low global integration), while random networks are defined by opposite attributes (low clustering, high global integration). Small-World graphs type (normal) lies in between these patterns, with clustering (connectivity) high and a few remote connections, so integration and functional segregation is ensured, complexity is achieved, as

well as numerical reduction of process steps, efficiency, low cost energy, adequate synchronization (Bullmore, 2009). In schizophrenia is found the destabilization of Small-World type graphs, the functional segregation of networks, the decrease of the number and activity of cortical association hubs (nodes), the increasing of the number and function of the non associative hubs (primary cortex and paralimbic), lower centrality of primary hubs (particularly a reduced central role for prime frontal hubs), the decreased connectivity of structural and functional areas of default network (default network is a functional network that captures the spontaneous brain activity), the high clustering in higher nodes (leading to congestion in the higher nodes that normally controls other nodes/hubs) (Bullmore, 2009, Rubinov, 2009, van den Heuvel, 2010, Micheloyannis, 2006).

The cardiovascular risk comes to add an overload of cognitive impairment for schizophrenic subjects; the cardiovascular etiopathogenesis was the most common cause of death for schizophrenia patients before acknowledgment of metabolic syndrome (Mortensen, 1990) and remains, alongside with cancer mortality, an important cause of death after 2005-2006 (Bushe, 2010). The sources of cardiovascular risk for schizophrenia subjects (Meyer, 2010) derive from: 1) antipsychotic treatment, as demonstrated by CATIE study that shows the high prevalence of cardiovascular risk in schizophrenia patients (Lieberman, 2011) and also a link between inflammatory markers that are involved in cardiovascular risk (Ridker, 2005) and the CATIE findings (Meyer, 2009); 2) high smoking prevalence in schizophrenia subjects (Brown, 1999); 3) poor access to health services (Folsom, 2002, Meyer, 2005) and undertreatment of medical conditions (Druss, 2000; Nasrallah, 2006); 4) schizophrenia associated metabolic dysfunction (van Nimwegen, 2008). There is also a link between inflammatory markers that are involved in cardiovascular risk (Ridker, 2005) and the CATIE findings.

Cognitive impairment is the cornerstone in etiopathogenesis of schizophrenia; it defines the global behavioral and functional expression of this disorder. Cognitive impairment arise from schizophrenia vulnerability and is catalyzed by the onset of the malady; it has several variants of evolution and it can be aggravated further by the cardiovascular engraft but also it can be improved by coping, compensation, decreased social pressure and cognitive recovery treatment. Whether it is conceptualized as dysconnectivity between functional compartments of the brain or aberrant connectivity of brain networks, cognitive deficit remains the most important predictor of functional outcome of patients with schizophrenia (Leung, 2008, Green, 2004).

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CORRELATION BETWEEN GLYCEMIC IMBALANCE IN ORAL DIABETIC TREATMENT AND DEPRESSION

Cristian Gabos Grecu¹, Theodor Moica², Melinda Ferencz^{1,2}, Elena Gabriela Buicu^{1,3},
Daniela Sabau^{1,2}, Iosif Gabos Grecu^{1,2}, Marieta Gabos Grecu^{1,2}

¹University of Medicine and Pharmacy, Tirgu Mures, Romania

²Psychiatric Clinic No 1, Tirgu Mures, Romania

³Mental Health Center, Tirgu Mures, Romania

Abstract

Introduction: Ever since the 17th century, the famous English physician T Willis has observed a high frequency of diabetes among patients who have had long depression moods, stressful life events, or have experienced different losses. Recent studies have confirmed what Willis described since the 17th century, proving that depressed patients have an increased risk developing type 2 diabetes compared to non-depressed population (5). Our purpose was to investigate the relationship between depression and Glycemic imbalance in patients with diabetes mellitus type 2 treated with oral agents. We assume that depression worsens the glycemic control through lack of self-care measures, lack of interest and pleasure, and treating depression can result in improved glycemic control.

Methods: Prospective study, conducted on a number of 30 patients with type 2 diabetes at the MEDIAB Centre in Targu Mures in collaboration with the specialized ambulatory of the Psychiatric Clinic No. 1, during the period September 2012- May 2013. The patients were administered daily doses of Duloxetine (up to 6 mg/day). In order to monitor the glycemic control the levels of glycosylated hemoglobin (HbA1c) were determined both at baseline and at the end of nine months of study. All patients had diabetic treatment, either oral antidiabetic or insulin, conducted by the diabetologist.

Results: As a result of the statistical processing of data, the resulting overall average age of the sample located at $M_{age} = 60.03$ years, with a standard deviation of 5.82 of which 15 patients are male ($M_{age} = 58.73$, $SD = 6.92$), and 15 patients are women ($M_{age} = 61.33$, $SD = 4.33$).

Discussion: In general, the effectiveness of antidepressants for pharmacotherapy in patients with diabetes mellitus has been the subject of several studies.

Conclusions: The treatment of depressive symptoms with Duloxetine 60 mg has the effect of improving glycemic control, translated by levels of HbA1c below 7%.

Key words: depression, diabetes type 2, glycemic imbalance.

¹ Correspondence: Elena Gabriela Buicu, Maramures St., no. 10, Tirgu Mures, Romania.
Tel.: +40 753 089789; e-mail: gabrielabuicu@yahoo.com.

Introduction

Even since the 17th century, the famous English physician T Willis has observed a high frequency of diabetes among patients who have had long depression moods, stressful life events, or have experienced different losses. Recent studies have confirmed what Willis described since the 17th century, proving that depressed patients have an increased risk developing type 2 diabetes compared to non-depressed population (5). In terms of Pathophysiology mechanism that may explain the growing risk of type 2 diabetes in patients with depression, were released several hypotheses, and one of them would be: increased activity of the hypothalamic-pituitary-adrenal function and of the sympathetic nervous system. It is known that throughout the life of people with diabetes they have accomplished many tasks such as: blood glucose self-monitoring, a daily diet, walking 30 minutes daily and last but not least diabetic treatment adherence, which helps maintain an optimal glycemic control for preventing complications.

Compliance with drug regimes and educational programs has proven effective in improving glycemic balance, but it does not happen to all patients. In the glycemic control there are several psycho-social, behavioral and medical barriers.

Depression is associated with an unfavorable evolution of diabetes, some evidence suggesting that depression disrupts the glycemic control through its symptomatology.

Patients with diabetes mellitus encounter a number of changes which require an appropriate coping mechanism: on one hand, integration into the daily life of diet, of the therapeutic regime, but also they have to deal with the threat or actual installation of diabetes mellitus complications, adaptation to the work place, and last but not least into the family (4). Throughout the evolution of diabetes, it is no wonder, that some patients are having emotional stress and substantial motivation problems. Exhaustion was highlighted, feelings of guilt, discouragement, burn-outs that have been correlated with poor glycemic control. Also physical inactivity and obesity, both behaviors being common in depression were correlated with insulin resistance.

The continuum in diabetes mellitus starts with insulin resistance, glucose intolerance and diabetes mellitus as a result of the inability to secrete insulin. Insulin resistance is defined as a sensitivity decrease of peripheral insulin receptors to insulin action, and, as a compensatory mechanism, to compensate for the reduced function of the peripheral receptor, beta pancreatic cells secrete increased levels of insulin released into the circulation. Insulin resistance is measured by the degree to which glucose is removed from the blood in response to a certain amount of insulin during fasting.

Determination of glycosylated hemoglobin is not used in the initial diagnosis of diabetes mellitus, because a normal level thereof does not exclude the diagnosis of diabetes. In people without diabetes mellitus, HbA1c normal values are between 4-6%. The 6.1%-4.0% interval corresponds to

prediabetes (a situation which must be investigated, since it is a reversible phase, in which the road to diabetes can be stopped), while values of 6.5% and over correspond to diabetes mellitus (7).

In general, most patients with diabetes mellitus should have HbA1c levels below 7%. The value of 7% is taken most often as part of a good glycemic control, the values below 7% being associated with a metabolic balance and a minimal risk of complications (mainly microvascular). The higher the glicate hemoglobin values are, one can say that the glycemic imbalance is greater, and thus increases the risk of complications. High glicate hemoglobin values always fire an alarm, which can mean, in many cases, the need to start treatment with insulin, to prevent an unfavorable evolution of diabetes (9).

Purpose

To investigate the relationship between depression and glycemic imbalance in patients with diabetes mellitus type 2 treated with oral agents. We assume that depression worsens glycemic control through lack of self-care measures, lack of interest and pleasure, and treating depression can have the effect of improving glycemic control.

Method

This research was conducted on a total of 30 patients with type 2 diabetes mellitus hospitalized in the MEDIAB Centre in Targu Mures in collaboration with the specialized ambulatory of the Psychiatric Clinic No. 1 during the period September 2012 - May 2013. Following the professional examination they were diagnosed with major depressive disorder, according to the diagnostic criteria DSM-IV-TR. For the assessment of the severity of depression we used the Hamilton scale with 17 items, introduced by M. Hamilton (1960) and depending on the score obtained, it classifies depression as follows: mild, medium, major. The scale reveals and highlights the global assessment of depression and anxiety in both in somatic and psychic plane.

The items composing the scale evaluate the affective mood, feelings of self-blame, autolytic ideation, insomnia, and anxious mood, cognitive and behavioral symptoms of depression, gastrointestinal symptoms, muscle tension as well as cardiovascular, genital-urinary, or vegetative symptoms. At this scale the patient can achieve a maximum score of 62 points. The minimum score is 0 points. A score between 8-17 points indicates the presence of a low level of depression, a score of 18-24 means a moderate level of depression and a score of more than 25 indicates a major level of depression. The scale differentiates healthy subjects from pathological, being mainly used when we want to measure the therapeutic effect after starting a certain type of treatment to determine the percentage of patients who have achieved substantial improvements or complete remission.

Patients were administered daily doses of Duloxetine (up to 60 mg/day).

Both initially and at the end of nine months of study, the levels of glycosylated hemoglobin (HbA1c) were determined in order to monitor the glycemic control. All patients had antidiabetic treatment, either oral antidiabetic or insulin and oral antidiabetic, headed by the diabetologist doctor.

For the interpretation of statistical data was used the statistical program SPSS 11. For the verification of normal distribution (Gaussian) of data, we used as concordance tests the Kolmogorov-Smirnov and D'Agostino-Pearson test. They helped us to distinguish the type of frequency within our sample. These concordance tests identify whether a sample comes from a statistic population that conform to a particular type of frequency distribution.

Results

As a result of the statistical processing of data, the resulting overall average age of the sample located at $M_{age} = 60.03$, with a standard deviation of 5.82, of which 15 patients are male ($M_{age} = 58.73$, $SD = 6.92$) and 15 patients are women ($M_{age} = 61.33$, $SD = 4.33$), therefore the research taking place on a sample of older patients (Table 1, Fig. 1).

Table 1. Distribution of the sample by age

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
AGE	30	48	70	60,03	5,828
MALE	15	48	70	58,73	6,923
FEMALE	15	53	68	61,33	4,337
Valid N (listwise)	15				

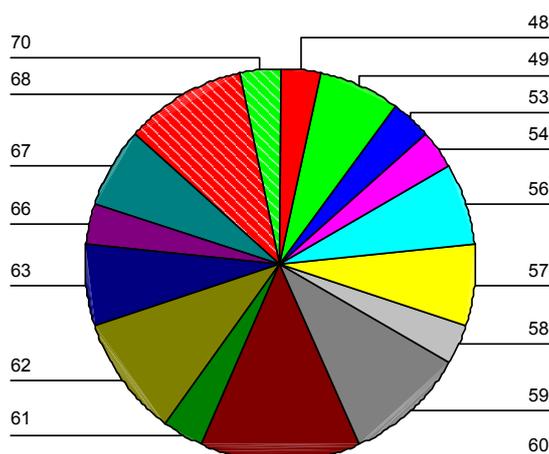


Fig. 1. Distribution of the sample by age

Analyzing the distribution of the determined HbA1C values, in patients in the initial phase, we emphasize the normal tendency of the distribution of values, resulting therefore a *symmetric* distribution of data. In the initial phase for the entire sample were obtained values of HbA1C, where $M = 8.1$, and $SD = 1,14$ (Fig. 2).

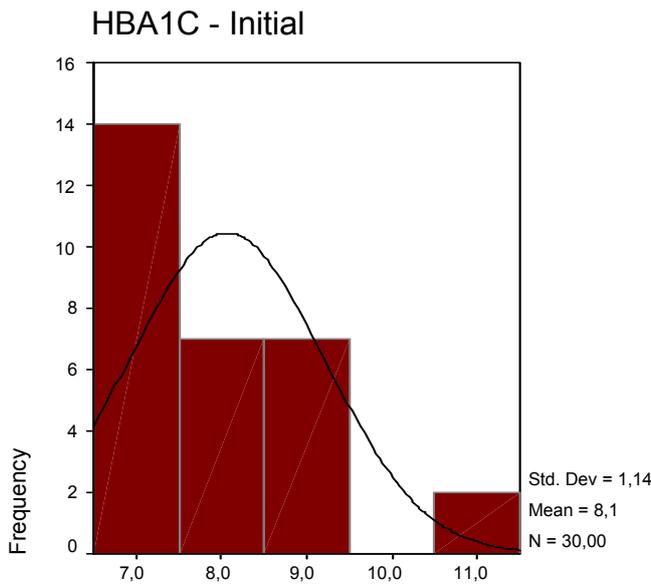


Fig. 2. Distribution of the batch depending on the initial values of HbA1C

Analyzing the distribution of the scores obtained by patients at the HAM-D survey in the initial phase, we emphasize the normal trend of the distribution of scores resulting therefore a *symmetric* distribution of data. In the initial phase for the entire sample was obtained in the HAM-D test, an overall score, where $M = 23.7$ and $SD = 1.70$ (Fig. 3).

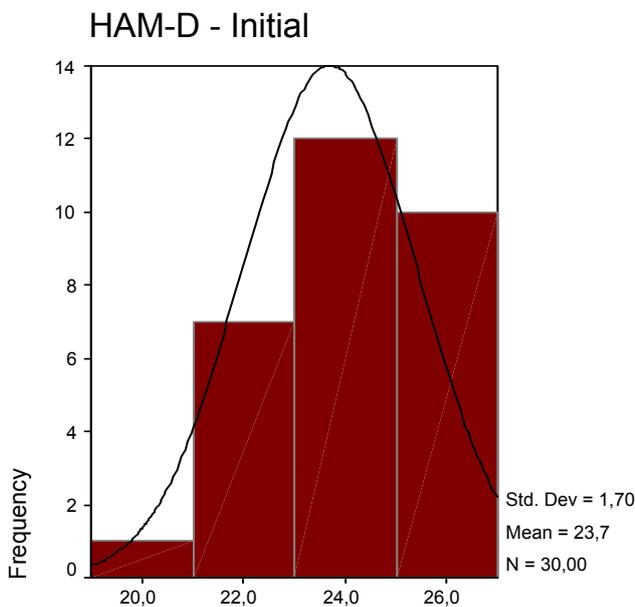


Fig. 3. Distribution of the batch depending on the initial scores of the HAM-D

Patients were administered daily doses of Duloxetine (up to 60 mg/day) throughout the period of the trial and finally was given the HAM-D survey and were reassessed the levels of glycosylated hemoglobin (HbA1c) in order to monitor the glycemic control in response to antidepressant treatment. Analyzing the distribution of the scores obtained by patients at the HAM-D test in the final phase, we emphasize the normal trend of the distribution of scores resulting therefore a *symmetric* distribution of data. In the final phase for the entire sample was obtained in the HAM-D test, an overall score, where $M = 9.1$, and $SD = 3.25$ (Fig. 4).

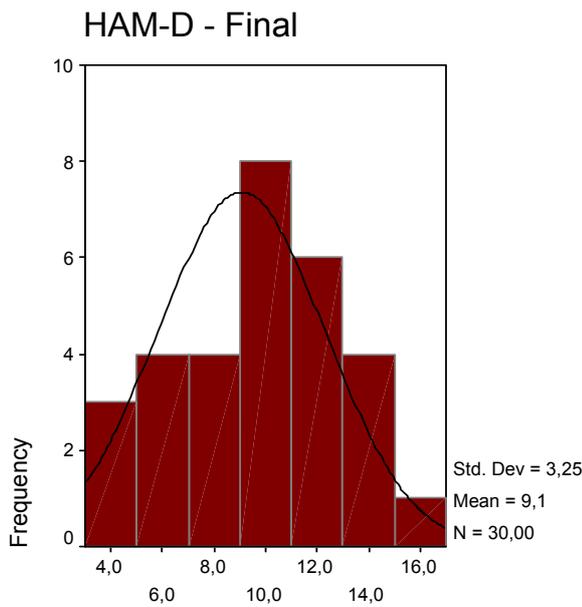


Fig. 4. Distribution of the batch depending on final scores at the HAM-D survey

Analyzing the distribution of HbA1C determined values, in patients in the final phase, we emphasize the normal trend of the distribution of scores resulting therefore a *symmetric* distribution of data. In the final phase for the entire sample was obtained in the HBA1C-final test, an overall score, where $M = 6.41$, $SD = 0.90$ (Fig. 5).

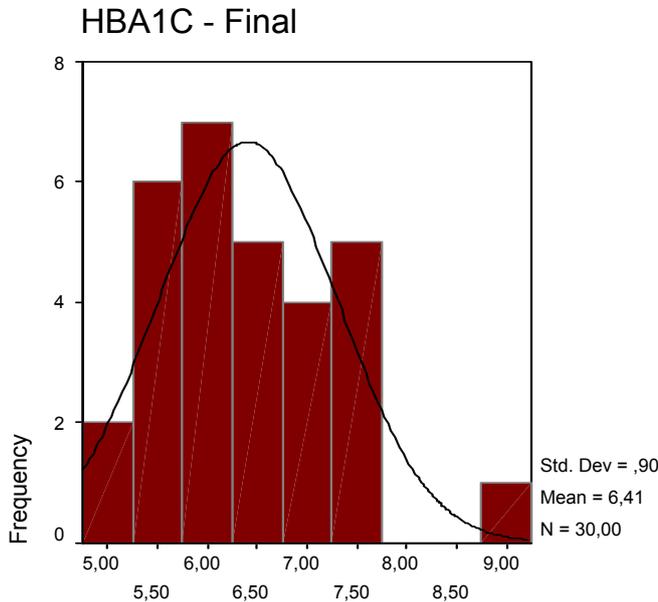


Fig. 5. Distribution of the batch depending on the final values of HbA1C

We assume that the existence of depression correlates with a glycemic imbalance, translated by elevated glicate hemoglobin high values. *Null hypothesis*: the medium not depressive episode is not associated with a glycemic imbalance.

The *Spearman* correlation coefficient between HBA1C and HAM-D is $r_{\text{Spearman}}(30) = -.42$, $p < .05$. Hence it follows that the probability of getting this correlation due to chance is less than 5%.

In conclusion, there is a moderate statistically significant positive correlation which demonstrates that the medium depressive episode is associated with a glycemic imbalance in the sample being investigated (Table 2).

Table 2. The correlation between HBA1C and HAM-D in the initial moment

			HBA1C	HAMDI
Spearman's rho	HBA1C	Correlation Coefficient	1,000	,426*
		Sig. (2-tailed)	,	,019
		N	30	30
	HAMDI	Correlation Coefficient	,426*	1,000
		Sig. (2-tailed)	,019	,
		N	30	30

*. Correlation is significant at the .05 level (2-tailed).

We assume that treating depression can have the effect of improving glycemic control.

Null hypothesis: the depressive symptoms treatment with Duloxetine 60 mg, does not have the effect of improving glycemic control, translated by levels of HbA1c below 7%.

Table 3. The correlation between HBA1C and HAM-D after antidepressant treatment

		HBA1CF	HAMDF
HBA1CF	Pearson Correlation	1	,702**
	Sig. (2-tailed)	,	,000
	N	30	30
HAMDF	Pearson Correlation	,702**	1
	Sig. (2-tailed)	,000	,
	N	30	30

** . Correlation is significant at the 0.01 level

The *Pearson* correlation coefficient between HbA1C and HAM-D is $r = .70$, $p < 0.01$. Hence it follows that the probability of getting this correlation due to chance is less than 1%. In conclusion, there is a statistically significant positive correlation, which demonstrates that improving scores on the scale the HAM-D is associated with a glycemic balance within the sample being investigated.

Discussion

In the light of the results we've obtained we have shown that the moderate depressive episode is associated with a glycemic imbalance, translated by elevated HbA1C values. Instead, in the final phase, at the end of nine months of study, as depression lowers, HbA1C values also normalize.

If in the initial phase the depression was located at a moderate level ($M = 23.7$), and glicate hemoglobin levels beyond the normal limit ($M = 8.1$), in the final phase, the depression dropped up to the light level ($M = 9.1$), simultaneous with the normalization of HbA1C values ($M = 6.41$). Thus we can say that there is a statistically significant negative correlation in the initial phase ($p < 0.05$) and then a significant statistical correlation in the final phase, the aftercare ($p < 0.01$). In other words as the depressive episode grows in intensity, there's a glycemimic imbalance, translated by high levels of glicate hemoglobin, and as the depression reduces up to the light level, the same thing happens with glicate hemoglobin values, which reduce to normal limits.

In a meta-analysis, whose goal was highlighting the association of depression with a low glycemimic control in patients with type 1 diabetes or type 2, Lustman and collab in 2000 (1) have found that depression was associated with statistically significant hyperglycemia ($Z = 5.4, < P 0.0001$), the treatment of depression rising the percentage of patients with an optimal blood glucose control, to 41-58%. This meta-analysis confirms the association of depression with hyperglycemia, but does not establish nor the mechanism nor the direction of the association. Depression can be a cause or a consequence of hyperglycemia, the causal mechanisms underlying depression may or may not be the same, the production mechanism may vary over time, between episodes, and individually (1).

Also, in a study of 8 weeks, Lustman and collab., (2) have noticed a reduction in symptoms of depression which was significantly higher in patients treated with fluoxetine, compared to those who received placebo (BDI, $_ 14.0$ vs $_ 8.8$, $P = 0.03$; HAMD, $_ 10.7$ vs $_ 5.2$, $P = 0.01$). The procentage of patients who achieved a significant improvement in depression on the BDI was also higher in the fluoxetine group (66.7 vs. 37%, $P = 0.03$). In addition, trends were observed towards a higher rate of remission of the depression (48.1 vs. 25.9%, $P = 0.09$ at HAMD) and a greater reduction in blood glucose ($_ 0.40$ vs $_ 0.07\%$, $P = 0.13$) for the fluoxetine group. Fluoxetine reduces the severity of depression in diabetic patients. The study showed that after only 8 weeks, treatment with Fluoxetine has resulted in a better glycemimic control. (2)

In general, the effectiveness of antidepressants as pharmacotherapy in patients with diabetes mellitus has been the subject of several studies. Nortriptyline hydrochloride, a tricyclic antidepressant, was the only previously tested agent, in a placebo-controlled study on patients with diabetes mellitus (3). Reduction of the depressive symptoms was significantly higher in patients treated with nortriptyline, compared to those treated with placebo, but the drug had significant negative effects on glycemimic control.

In patients treated with new classes of antidepressants, such as selective serotonin reuptake inhibitors (SSRI) (6) hyperglycemia was not reported.

Tollefson et al (8) found that fluoxetine was less effective in patients older than 60 years, a result that might be due to the existence of medical co-morbidities in this age group. The efficacy of

antidepressant treatment may be limited by the restrictive lifestyle, pain, functional disability and incapacity-problems that often accompany diabetes in the advanced form (3).

Lewko et al (4) in the study that evaluated the occurrence of symptoms of anxiety and depression in patients with type 2 diabetes, as well as the relationship between the occurrence of anxiety and depression symptoms, quality of life, and the level of acceptance of the disease, found out that the symptoms of anxiety and depression would negatively affect the degree of acceptance of the disease and reduce significantly the quality of life in patients with diabetes mellitus.

Conclusion

For a more realistic knowledge of the prevalence of depressive disorders in patients with type 2 diabetes, an universal screening program and for clinical and epidemiological studies could be useful. The diabetologist may be the first professional to observe and to require the collaboration of a psychiatrist in order to clarify the diagnosis and early antidepressant treatment. Taking Duloxetine, in adequate doses, 60 mg/day over a sufficient period of time provides the best chance for healing, and the maintenance therapy administered at the same dose as for the treatment of the acute phase of depression, ensures relapse prevention. Depressive symptoms treatment with Duloxetine 60 mg, has the effect of improving glycemic control, translated by levels of HbA1c below 7%.

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