CASE REPORT

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

A rare case of Meckel–Gruber syndrome

DANIELA VERONICA CHIRIAC[1)], LAVINIA MARIA HOGEA[2)], ANA CRISTINA BREDICEAN[3)], ROBERT REDNIC[4)], LAURA ALEXANDRA NUSSBAUM[5)], GHEORGHE BOGDAN HOGEA[6)], MIRELA LOREDANA GRIGORAŞ[7)]

[1)]*Discipline of Obstetrics–Gynecology, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania*

[2)]*Discipline of Psychology, Department of Neurosciences, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania*

[3)]*Discipline of Psychiatry, Department of Neurosciences, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania*

[4)]*Clinic of Obstetrics–Gynecology, Emergency Municipal Hospital, Timişoara, Romania*

[5)]*Discipline of Pedopsychiatry, Department of Neurosciences, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania*

[6)]*Discipline of Orthopedics and Trauma, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania*

[7)]*Discipline of Anatomy and Embryology, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania*

Abstract

Meckel–Gruber syndrome (MKS) is a lethal, autosomal recessive transmitted anomaly, characterized by the ultrasound triad: occipital meningoencephalocele, bilateral polycystic kidney, postaxial polydactyly. The incidence is between 1/13 250 and 1/140 000 live births, being a rare anomaly. We report a MKS case of feminine gender diagnosed on two ultrasound findings (bilateral polycystic kidney, occipital meningoencephalocele). This case highlights the presence of MKS in a young female without family history.

Keywords: Meckel–Gruber syndrome, ultrasound, polycystic kidney, meningoencephalocele, postaxial polydactyly.

Introduction

Meckel–Gruber syndrome (MKS), is a lethal, autosomal recessive disorder characterized by central nervous system (CNS) malformations (typically occipital meningoencephalocele), bilateral renal cystic dysplasia, hepatic ductal proliferation, fibrosis and cysts, and polydactyly [1, 2].

MKS is characterized by the following ultrasound (US) triad: polycystic kidneys (present in 95–100% of the US examinations), occipital encephalocele (60–80%) and postaxial polydactyly (55–75%) [3, 4].

The worldwide incidence of the disease varies from 1/1304 in Gujarati Indians [5] to 1/140 000 in Great Britain [6]. High rates were found in Belgium and Finland (1/9000 births) [1]. There is evidence that prevalence is higher in populations with higher consanguinity rates, as India [5, 7], Pakistan [8], Kuwait and other Arabian countries [9, 10]. Genetically, MKS is known to be a heterogeneous disease with linkage to five loci and four genes identified so far. All the genes are associated with ciliary functions. Mutations in ciliary genes are known to cause a number of human monogenic disorders that are collectively known as ciliopathies, disorders with overlapping clinical features. An especially interesting aspect of ciliary diseases is that they range from embryonically lethal Meckel syndrome to less severe multisystem disorders, such as Bardet–Biedl syndrome, where the patients suffer from obesity, retinal degeneration, polydactyly, mental retardation, and cystic kidneys, for example.

In 1822, the German anatomist Johann Friedrich Meckel (1781–1833) first described two newborn siblings, a female and a male, that died of identical malformations of occipital meningoencephalocele, polycystic kidneys, polydactyly, and cleft palate. In 1934, Georg Benno Gruber (1884–1977) reported several familial cases with encephalocele, polycystic kidneys, and polydactyly using a disease name "dysencephalia splanchnocystica", and suggested a genetic origin of the disease. In 1969, Opitz & Howe delineated the clinical features and proposed a disease name "Meckel syndrome" [11].

MKS is classified based on the chromosome were the gene mutation is placed: MKS type I (gene mutation on chromosome 17), MKS type II (gene mutation on chromosome 11), MKS type III (gene mutation on chromosome 8) [12].

MKS was frequently reported in consanguineous marriages, affecting both sexes equally.

Case presentation

A 15-year-old primigravida, 29 weeks of gestation, with unremarkable family history was admitted in our Hospital with the diagnosis of oligohydramnios. She was previously diagnosed with oligohydramnios in a level I center, then transferred to our Unit.

US examination revealed: severe oligohydramnios (amniotic fluid index 2 cm) bilateral polycystic kidneys (occupying the entire fetal abdomen) (Figure 1, A and B). Skull US revealed: normal parenchyma, moderate unilateral ventriculomegaly, interhemispheric cyst, and bone defect in the posterior region of the calvarium with herniation of the brain (approximate 3/3 cm occipital encephalocele) (Figure 2, A and B). Fetal profile revealed micrognathia (Figure 3).

Based on the two characteristic ultrasound elements (polycystic kidneys and occipital encephalocele), we suspected the presence of MKS. We searched for the third element (postaxial polydactyly), but we could not reveal that due to severe oligohydramnios.

For differential diagnosis with trisomy 13, we performed cordocentesis with assessment of the fetal karyotype (that turned out to be normal 46XX) (Figure 4).

The patient was informed that the US findings are incompatible with life and might indicate the consequence of recessively inherited gene mutations (e.g., Meckel–Gruber syndrome). In order to detect the gene mutation, prenatal genetic counseling is paramount for future pregnancies. Given the fact that this syndrome has a mortality rate of 100%, with most fetuses surviving only a few days to weeks, we advise termination of the pregnancy with the signed consent of the legal guardians of the mother. She elected immediate termination of pregnancy. We induced labor using Prostaglandin E2. The patient gave birth to a female fetus weighing 2000 g that died in the first hour after birth.

Physical examination of the fetus revealed: occipital encephalocele, micrognathia and postaxial polydactyly of the upper and lower limbs (Figures 5–8).

The autopsy was not performed because the legal conditions were not meet.

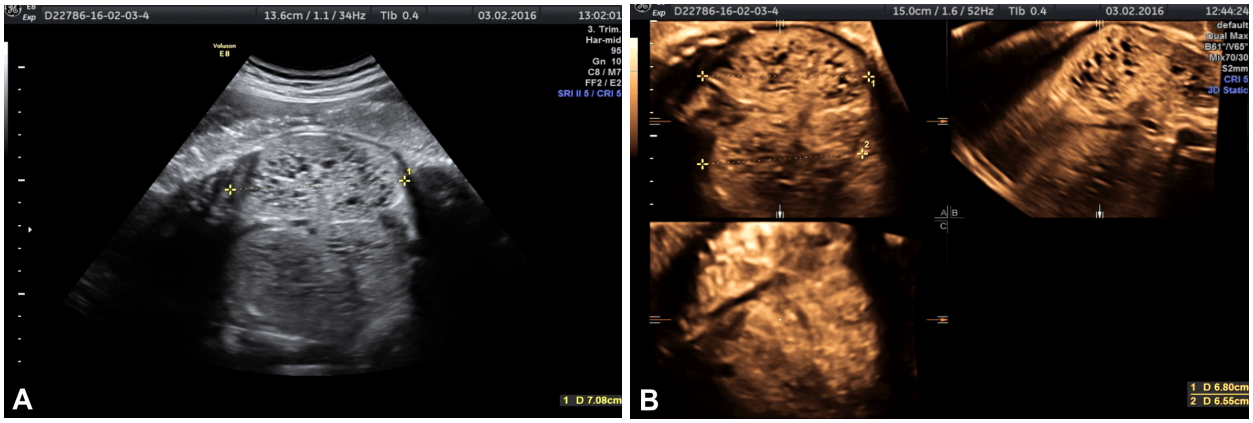

Figure 1 – ***(A) Transverse view of the fetal abdomen, note the enlarged dysplastic cystic kidneys; (B) Transverse view of the fetal abdomen, note the enlarged dysplastic cystic kidneys (3D acquisition).***

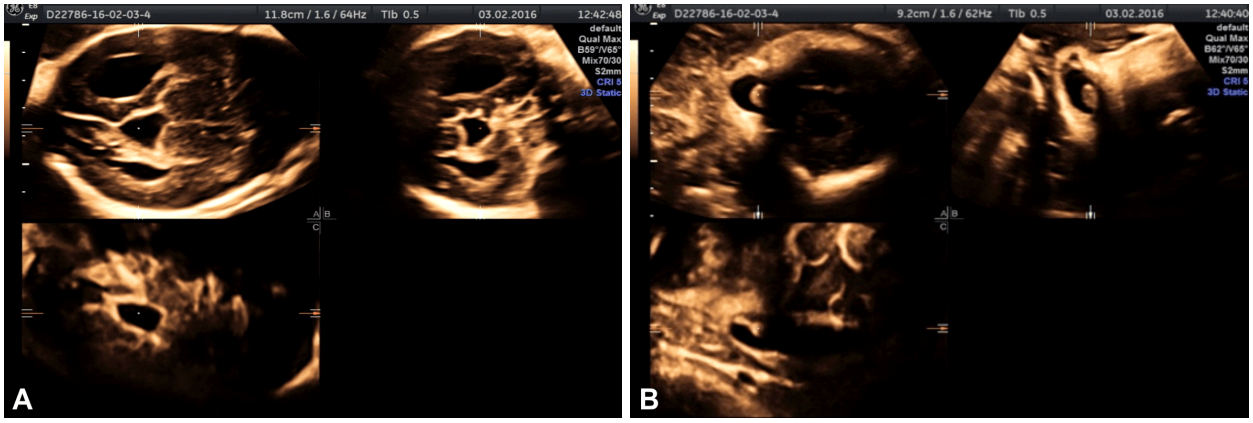

Figure 2 – ***(A) Transthalamic section of the brain protruding through a posterior calvarial defect (encephalocele, 3D); (B) View of the brain protruding through a posterior calvarial defect (3D acquisition).***

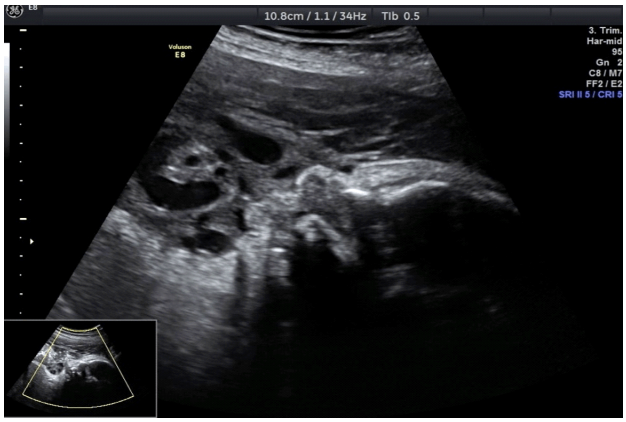

Figure 3 – ***Fetal profile showing micrognathia.***

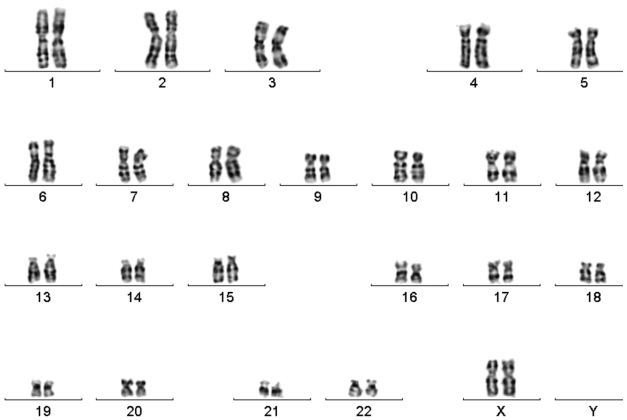

Figure 4 – ***Normal karyotype (46XX) obtained through cordocentesis.***

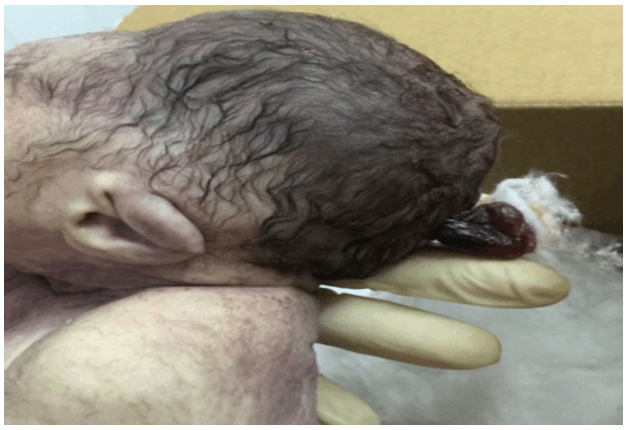

Figure 5 – ***Occipital encephalocele in 29 weeks old fetus.***

Figure 6 – ***Profile of the fetus showing micrognathia.***

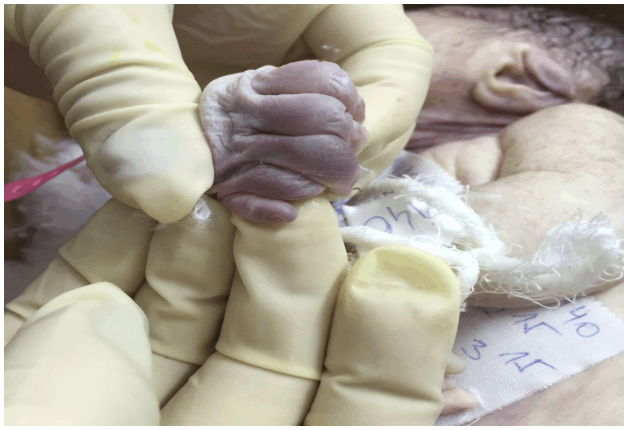

Figure 7 – ***Postaxial polydactyly of upper limb.***

Figure 8 – ***Postaxial polydactyly of lower limbs.***

Discussion

MKS is a recessive condition, most commonly characterized by cystic kidneys, posterior encephalocele, polydactyly and hepatic fibrosis.

The largest study regarding the prevalence of MKS, conducted between 1990–2011, based on 34 EUROCAT (*European Registration of Congenital Anomalies and Twins*) reported 191 cases of MKS per 5 483 380 births [13]. According with *National Organization for Rare Disorders* (NORD), until 2016 only 200 cases of MKS have been reported in the literature [11, 12].

Recent advances in molecular genetic diagnosis have shown that MKS can be caused by mutations in thirteen genes [12, 14]. Importantly, it is now clear that all of the genes involved in MKS affect the structure or function of the cilium, a hair-like organelle present on the surface of most cell types. Recently, diseases due to disorders of the structure and/or function of the cilium have been termed 'ciliopathies'. Therefore, MKS is best thought of as being part of the large spectrum of 'ciliopathies' disorders that includes MKS, Joubert syndrome, COACH (cerebellar vermis hypoplasia, oligophrenia, ataxia, coloboma, hepatic fibrosis) syndrome, nephronophthisis, Senior–Løken syndrome and others [15].

Among the ciliopathies, MKS manifests with the most striking fetal malformations, making it amenable to diagnosis by prenatal imaging. Ultrasonographic prenatal diagnosis of MKS was first accomplished in 1982. Over the ensuing years most reported prenatal diagnoses have been in the second trimester, although first-trimester diagnoses have been described as well [16]. In general, confirmation of the diagnosis of MKS has been based on pathological findings and family history.

MKS can be suspected from 14 weeks of gestation due to the presence of oligohydramnios. Determination of AFP (alpha-fetoprotein) in the amniotic fluid at 12 weeks of gestation can be useful to detect neural tube abnormalities (encephalocele) [3].

Besides the classical US triad, which is almost consistently present, other malformations can be found:

- CNS: microcephaly, anencephaly, holoprosencephaly, hydrocephaly, polymicrogyria, agenesis of the corpus callosum;
- face: micrognathia, cleft palate, hypertelorism, microphthalmia;
- heart: atrial septal defect, ventricular septal defect, patent ductus arteriosus.

MKS may be associated with Dandy–Walker and Arnold–Chiari malformations [16, 17]. The differential diagnosis should be made with the following conditions: trisomy 13 (requires karyotyping – which was performed in our case report), Larsen syndrome, Smith–Lemli–Opitz syndrome (caused by deficiency of the enzyme 7-dehydrocholesterol-Δ^7-reductase), Bardet–Biedl syndrome (no CNS abnormalities) [1, 14, 18], Joubert syndrome – the last two syndromes are part of the same ciliopathies as MKS [19]. It is an autosomal recessive (AR) disease with 25% chance of recurrence at each pregnancy [1, 11].

With a mortality of 100%, once the diagnosis is certain, termination of the pregnancy is recommended and genetic counseling due to the risk of recurrence [1, 11].

It is a lethal anomaly – most fetuses are born dead or die within the first hours of life due to kidney dysfunction and pulmonary hypoplasia.

Psychological counseling

The patient received counseling during 14 sessions in order to reduce the level of anxiety and emotional distress and to prevent depression. The whole intervention should be in an ethical, non-stigmatizing frame, taking into account the fact that the patient is still an adolescent [20]. If needed, when prescribing medication, the pharmacological intervention should be personalized and carefully chosen in function of the genetic, pharmacogenetic and psychological profile of the patient, in order to prevent potential adverse events and for improved life quality [21–23].

Cognitive restructuring techniques, breathing and relaxation control techniques (Schultz's autogenous training) were applied [24].

During therapy, the patient completed a personal diary in which she described daily personal experiences, results of exercises and themes.

Conclusions

The case we present is unusual, because it was diagnosed in the second trimester but also because it occurred in a low-risk patient with no prior history. Autopsy and genetic analysis (when available) represents the gold standard for the diagnosis. Unfortunately, in our case the autopsy could not be performed due to failure to meet the legal criteria.

Conflict of interests

The authors declare no conflict of interests.

Author contribution

Ana Cristina Bredicean has equal contribution and thus shares first authorship.

References

[1] Chen CP. Meckel syndrome: genetics, perinatal findings, and differential diagnosis. Taiwan J Obstet Gynecol, 2007, 46(1): 9–14.

[2] Dowdle WE, Robinson JF, Kneist A, Sirerol-Piquer MS, Frints SG, Corbit KC, Zaghloul NA, van Lijnschoten G, Mulders L, Verver DE, Zerres K, Reed RR, Attié-Bitach T, Johnson CA, García-Verdugo JM, Katsanis N, Bergmann C, Reiter JF. Disruption of a ciliary B9 protein complex causes Meckel syndrome. Am J Hum Genet, 2011, 89(1):94–110.

[3] Aslan K, Külahçı Aslan E, Orhan A, Atalay MA. Meckel Gruber syndrome, a case report. Organogenesis, 2015, 11(2):87–92.

[4] Sepulveda W, Wong AE, Andreeva E, Odegova N, Martinez-Ten P, Meagher S. Sonographic spectrum of first-trimester fetal cephalocele: review of 35 cases. Ultrasound Obstet Gynecol, 2015, 46(1):29–33.

[5] Young ID, Rickett AB, Clarke M. High incidence of Meckel's syndrome in Gujarati Indians. J Med Genet, 1985, 22(4):301–304.

[6] Seller MJ. Meckel syndrome and the prenatal diagnosis of neural tube defects. J Med Genet, 1978, 15(6):462–465.

[7] Panduranga C, Kangle R, Badami R, Patil PV. Meckel–Gruber syndrome: report of two cases. J Neurosci Rural Pract, 2012, 3(1):56–59.

[8] Crawfurd MdA, Jackson P, Kohler HG. Meckel's syndrome (dysencephalia splanchno-cystica) in two Pakistani sibs. J Med Genet, 1978, 15(3):242–245.

[9] Farag TI, Usha R, Uma R, Mady SA, al-Nagdy K, el-Badramany MH. Phenotypic variability in Meckel–Gruber syndrome. Clin Genet, 1990, 38(3):176–179.

[10] Teebi AS, al Saleh QA, Odeh H. Meckel syndrome and neural tube defects in Kuwait. J Med Genet, 1992, 29(2):140.

[11] Parelkar SV, Kapadnis SP, Sanghvi BV, Joshi PB, Mundada D, Oak SN. Meckel–Gruber syndrome: a rare and lethal anomaly with review of literature. J Pediatr Neurosci, 2013, 8(2):154–157.

[12] Attie-Bitach T. Hôpital Necker-Enfants Malades et Institut Imagine (INSERM), Paris, France, National Organization for Rare Disorders (NORD), 1989, 1996, 2003, 2016, https://rarediseases.org/rare-diseases/meckel-syndrome/; Meckel syndrome. Genetics Home Reference, US National Library of Medicine, National Institutes of Health, https://ghr.nlm.nih.gov/condition/meckel-syndrome, Last update: June 14, 2016.

[13] Barisic I, Boban L, Loane M, Garne E, Wellesley D, Calzolari E, Dolk H, Addor MC, Bergman JE, Braz P, Draper ES, Haeusler M, Khoshnood B, Klungsoyr K, Pierini A, Queisser-Luft A, Rankin J, Rissmann A, Verellen-Dumoulin C. Meckel–Gruber syndrome: a population-based study on prevalence, prenatal diagnosis, clinical features, and survival in Europe. Eur J Hum Genet, 2015, 23(6):746–752.

[14] Jones D, Fiozzo F, Waters B, McKnight D, Brown S. First-trimester diagnosis of Meckel–Gruber syndrome by fetal ultrasound with molecular identification of CC2D2A mutations by next-generation sequencing. Ultrasound Obstet Gynecol, 2014, 44(6):719–721.

[15] Tallila J, Jakkula E, Peltonen L, Salonen R, Kestilä M. Identification of CC2D2A as a Meckel syndrome gene adds an important piece to the ciliopathy puzzle. Am J Hum Genet, 2008, 82(6):1361–1367.

[16] Kitova TT, Kilova KP, Kitov BD, Masmoudi A, Milkov DA, Gaigi SS. A fetus with Meckel–Gruber syndrome associated with isomerism. Cent Eur J Med, 2014, 9(3):481–484.

[17] Karasu Y, Ülker K, Bozkurt M, Gençdal S, Çiçek M, Dede S, Özakşit G. Meckel Gruber syndrome diagnosed in two consecutive pregnancies. Proc Obstet Gynecol, 2015, 4(3): 7.

[18] Karmous-Benailly H, Martinovic J, Gubler MC, Sirot Y, Clech L, Ozilou C, Auge J, Brahimi N, Etchevers H, Detrait E, Esculpavit C, Audollent S, Goudefroye G, Gonzales M, Tantau J, Loget P, Joubert M, Gaillard D, Jeanne-Pasquier C, Delezoide AL, Peter MO, Plessis G, Simon-Bouy B, Dollfus H, Le Merrer M, Munnich A, Encha-Razavi F, Vekemans M, Attié-Bitach T. Antenatal presentation of Bardet–Biedl syndrome may mimic Meckel syndrome. Am J Hum Genet, 2005, 76(3): 493–504.

[19] Boycott KM, Parboosingh JS, Scott JN, McLeod DR, Greenberg CR, Fujiwara TM, Mah JK, Midgley J, Wade A, Bernier FP, Chodirker BN, Bunge M, Innes AM. Meckel syndrome in the Hutterite population is actually a Joubert-related cerebello-oculo-renal syndrome. Am J Med Genet A, 2007, 143A(15):1715–1725.

[20] Nussbaum L, Ogodescu A, Hogea L, Nussbaum L, Zetu I. Risk factors and resilience in the offspring of psychotic parents. Revista de Cercetare şi Intervenţie Socială, 2017, 56:114–122.

[21] Nussbaum L, Andreescu N, Hogea LM, Muntean C, Ştefănescu R, Puiu M. Pharmacological and clinical aspects of efficacy, safety and tolerability of atypical antipsychotic medication in child and adolescent patients with schizophrenia and bipolar disorders. Farmacia, 2016, 64(6):868–875.

[22] Andreescu N, Nussbaum L, Hogea LM, Grădinaru R, Muntean C, Ştefănescu R, Puiu M. Antipsychotic treatment emergent adverse events in correlation with the pharmacogenetic testing and drug interactions in children and adolescents with schizophrenia and bipolar disorder. Farmacia, 2016, 64(5):736–744.

[23] Nussbaum LA, Hogea LM, Andreescu NI, Grădinaru RC, Puiu M, Todica A. The prognostic and clinical significance of neuroimagistic and neurobiological vulnerability markers in correlation with the molecular pharmacogenetic testing in psychoses and ultra high-risk categories. Rom J Morphol Embryol, 2016, 57(3):959–967.

[24] Walker AP. The practice of genetic counseling. In: Baker DL, Schuette JL, Uhlmann WR (eds). A guide to genetic counseling. 1st edition, Wiley-Lisss, New York, 1998, 1–20.

Corresponding author
Lavinia Maria Hogea, Assistant Professor, PhD, Discipline of Psychology, Department of Neurosciences, "Victor Babeş" University of Medicine and Pharmacy, 14 Tudor Vladimirescu Street, 300173 Timişoara, Timiş County, Romania; Phone +40745–042 035, Fax +40256–215 241, e-mail: laviniahogea@yahoo.com

Received: September 5, 2016

Accepted: September 25, 2017