ABOUT

The **Romanian Journal of Rare Diseases**© is an international journal addressing rare diseases and orphan drugs from the perspectives of basic and clinical genetics, molecular genetics, cytogenetics, epigenetics, population genetics, biotechnology, neurogenetics, cardiogenetics, oncogenetics, pharmacogenetics and related fields, by publishing original works, review articles, clinical reports and other contributions from all areas covered by The **Romanian Journal of Rare Diseases**©. This publication is the international official journal of the National Committee for Rare Diseases, founded and started as part of the project of the Romanian Prader Willi Association, "The Norwegian-Romanian Partnership (NoRo) for progress in Rare Diseases" funded by the Norwegian Government granted by the Norwegian Cooperation Program for growth and sustainable development in Romania. The Romanian Prader Willi Association and the „Victor Babes” Publishing House, E. Murgu Square 2, 300041, Timisoara, tel./fax.0256220479, publish the journal quarterly

PURPOSE & AREA OF INTEREST

For the journal are of interest articles from basic and clinical research. The journal publishes original articles, short reports, special communications, provided that they are based on adequate experimental evidence, clinical studies, case reports, images in rare diseases, letters to the editor, book reviews, reports of congresses and other articles that will be brought to Editorial Board’s attention based on the public’s for the journal. Editorials are published by invitation but we look forward to be offered such material from researchers with experience and results in the study of rare diseases. Requirements for publication in the Romanian Journal of Rare Diseases are in accordance with the requirements of "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" 5th Edition. JAMA 1997, 277:927-934.

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GENETICS EDUCATION FOR DENTAL STUDENTS

Dragos T. Stefanescu¹, Nina Scribanu², Emilia Severin³

¹. Genetic Lab., Bucharest, Romania
². Georgetown Univ. Medical Ctr, Washington, DC, U.S.A.
³. Carol Davila Univ. Med. Pharm., Bucharest, Romania

Abstract
The information provided by deciphering of human genome sequences had positive effects on medical theory and practice and in dentistry. A PubMed search for appropriate articles and clinical cases grown our genetics department provided many examples of gene mutations that cause isolated inherited dental anomalies, mutations with pleiotropic effects and of genetic testing for oral cancer susceptibility and presymptomatic diagnosis of periodontal disease. We have used these to train students and residents to understand the impact of genetic modifications on oral health, to recognize genetically-determined or environmentally-induce anomalies, to become familiar with the genetic tests available to identify the cause of diseases or abnormalities of craniofacial complex and to provide patients with the best treatment possible based on genetic profile and offer them a genetic counseling.

Key Words: dental education, post-genomic era, dental students, dental residents.

Background
The deciphering of the human nuclear and mitochondrial genome sequences has had positive effects on medical theory and practice in all medical specialties, including dentistry. Nowadays, in Post-Human Genomic Era, the use of genetics in dental education and practice is a challenge and a new approach that focuses on diagnosis and management of patients and their families with genetically determined conditions that involve craniofacial and dento-alveolar structures. Both patients and their families want to know and understand what caused their dental or craniofacial disorders. These should change the education by focusing on implications and applications of genetic knowledge to dental health and patient care and by facilitating the integration of genetics in education and training of dental professionals.

The great majority of dental health specialists recognize the importance and potential of genetic and genomic evaluations in the future, but little has been done to incorporate this knowledge extensively in clinical practice. More then that, quite a few physicians suggested that dental disorders are common but not lethal for patients. Thus, the subject is not of broad interest to genetic medicine research and is slow-moving field of medical genetics.

The Events
In April 2003, on the 50th anniversary of the discovery of the double helical structure of DNA by J. Watson and F. Crick, the international consortium for the sequencing of the Human Genome reported on the achievement of the goals set by Human Genome Project [1]. This marked the beginning of an Era in which bioinformatics, biotechnology and genomics provide new perspectives and opportunities for understanding human pathology and generate new circumstances for prevention, diagnosis and treatment of hereditary diseases. The development of predictive medicine based on anticipatory prenatal
and pre-morbid studies and of a personalized medicine should permit individualized treatment based on a patient’s DNA profile.

The Facts
Concerned with the slow pace with which these new advances were being integrated within and between dental specialties, a call was published for genetics and genomics to play a vital role in research pertaining to oral health as well as in the practice of dentistry [2]. The Medical Center of Columbia University initiated a “Macy Study” to explore new education models and strategies instrumental for the introduction of genetics in dental school curriculum [3-6] and offered recommendations for a new curriculum in universities, for the student evaluation process, for the training of directors in clinical education, and for faculty building. The National Coalition for Health Professionals Education in Genetics (NCHPEG) has also promoted the education of health professionals in the advances in human genetics through the website called “Genetics, Disease and Dentistry”, www.nchpeg.org/dental, so as to help dental health professionals to integrate the advances of genetics in their practice. The large number of oral-dental-craniofacial anomalies and diseases reported in the literature [7-11] provides a strong reason for increased education in genetics for dental students. These disorders affect millions of people worldwide. The National Institute of Dental and Craniofacial Research (NIDCR) estimated that in United States there is a child born every 5 minutes with a craniofacial defect. The contribution of heredity in development of dental cavities, periodontal disease, oral cancers, anomalies of number, structure, shape, size or eruption of teeth, and other oral pathology has become evident [12-19]. For example, tooth agenesis, one of the most common dental anomalies, tends to run in families suggesting a genetic cause. We have studied over 100 patients with isolated congenitally missing teeth and found the tooth agenesis pattern (number and distribution of missing teeth) to be non-specific and in the majority of cases was inherited as an autosomal dominant trait. Individuals within the same family would be expected to have the same mutant genes and their different phenotypes to be an expression of gene variation [21]. The importance of genetic factors is shown by appearance of multiple cases among relatives (familial clustering) and higher concordance in identical than in non-identical twins. Mutation in a single gene may have pleiotropic effects and produce frequent association of several congenital anomalies. For example, the mutations of RUNX2 gene on chromosome 6p21 are associated with cleidocranial dysplasia (CCD) and multiple supernumerary teeth [18]. One of our patients, an 18-year-old girl, met the major diagnostic criteria of CCD: brachicephaly, prominent forehead, aplasia of both clavicles and abnormal shoulder movements, and multiple supernumerary teeth. Patient had no history of the disorder in her family. Based on clinical findings, the dentist referred the patient to genetic counseling. The analysis of the entire RUNX2/CBFA1 coding sequence by PCR amplification of fragments of genomic DNA identified a de novo mutation R225W that is typical for CCD [19] confirmed the clinical diagnosis and clarified the genetic status of the patient. The disease was caused by a de novo mutation. Another example is the mutation in the SH3BP2 gene at 4p16.3 that is associated with cherubism. One of our patients, a 9-year-old girl presented with mild, bilateral, progressive, painless and a little asymmetrical enlargement of the mandible. Dental problems included dislocated teeth, premature loss of deciduous teeth and misplaced unerupted permanent teeth. Clinical findings, biopsy and imaging tests suggested the diagnosis. There was no family history of similar findings. The maxillofacial surgeon suspected a non-familial cherubism and molecular genetic testing revealed a c.1244G>A mutation in exon 9 of the SH3BP2 gene [20] in both patient and her asymptomatic mother [25].
In both the above examples, genetic counseling provided information on cause, inheritance, and implications of genetic disorders to help patients and their families make informed medical and personal decisions. The results of molecular genetic tests were useful for diagnosis confirmation, follow-up and treatment of manifestations if necessary and for prevention of dental anomalies in the next generation of children.

Many oral-dental-craniofacial disorders are phenotypically similar but genetically heterogeneous. Similarly, the same gene mutation may cause phenotypes of different severity. Abnormal craniofacial phenotypes are caused by inherited genetic defects or result from spontaneous genetic mutations. Advances in molecular genetics have been essential for the identification of genes involved in oral and craniofacial pathogenesis (Table 1). Gene mapping may help dentists know which patient is susceptible to what type of anomalies. The National Center for Biotechnology Information (NCBI), one of the Centers of NIH, recognizes 1,250 gene loci for craniofacial diseases and disorders. A systematic search on Online Mendelian Inheritance in Man (OMIM) database will help students, residents or dental professionals to find information about a particular genetic disorder and relationship between clinical phenotype and genotype.

Oro-dental and craniofacial abnormalities may be genetically determined or may be environmentally induced, systemic or local changes or by a combination of these factors. The genetic studies concerning the non-syndromic and syndromic orodento-craniofacial anomalies contribute to the understanding of the genotype-phenotype correlations and of the way in which the changes of genetic structure produce a significant clinical variability of these anomalies which are facing the clinician. The past research studies identified single-gene mutations that cause craniofacial defects associated with mendelian diseases, such as osteogenesis imperfecta, dentinogenesis imperfecta II, ectodermal dysplasias, DiGeorge syndrome. Recent studies are focused on complex disorder which are more common than mendelian diseases and caused by multiple genes interacting with each other and with environmental factors. An example is non-syndromic cleft lip with or without cleft palate (CL/P) that affects more than one child per 1000 births.

Genetic research feeds back to the clinical services allowing the development of new diagnostic tests, novel prevention and therapeutic strategies.

**How should be Dental Students and Residents trained?**

Educators and academic staff should provide the opportunity for dental students and residents (especially residents in pediatric dentistry, orthodontics or oral pathology) to learn how to translate genes into dental health. This means some changes in Dental Curriculum structure [10]. Basic genetics lectures followed up by clinical genetics instruction help to develop self-concept of student, practice of knowledge and skills. In our country, like in other European countries, Dental Curriculum structure includes training stages in basic and medical genetics but the quantity and quality of genetic information vary greatly from a school of dentistry to another [22]. Our School of Dentistry incorporated genetics teaching into its own Curriculum. Genetics Curriculum focuses on learning the structure, function and regulation of the genome and applying genetic information to a wide variety of clinical problems in dental medicine and patient care. Learning within clinical teams, self-directed learning, courses with an associated laboratory and research experience are encouraged.

Nowadays, through mass media and the Internet information regarding the genetic research reaches patients quickly. The dentist should be prepared to understand the impact of the genetic variability on oral health, be aware of the available genetic testing in order to identify the genetic cause of a disease or anomaly, offer the patient with or
without genetic condition the best treatment possible related to the individual genetic characteristics and know where to refer the patients for genetic counseling. That is why, in the post-genomic era, the assessment of the oral, dental and craniofacial pathology should be realized through interdisciplinary evaluations.

During their education and training programs in basic genetics, clinical cytogenetics, clinical molecular genetics and medical genetics, dental students and residents acquire genetic knowledge and skills to diagnose, manage and treat patients with genetic health problems.

**The Near Future**

Genetic screening for the identification of population groups at risk for oral cancer is not yet in routine practice, but its utilization could create ethical, legal and social issues similar to those encountered in screening for cystic fibrosis, sickle cell anemia, phenylketonuria, etc.

A better understanding of the molecular basis for cariogenicity could provide novel strategies for identification of individuals at high risk of developing carious lesions as well as suggesting additional preventive therapies [23].

The development of new treatment methods for the oral, dental and craniofacial disorders has revealed the regenerative potential of the stem cells isolated from the dental pulp of the deciduous teeth [24]. It was observed that these cells grow well in cultures and have potential to form dental bone and neural cells. They can be utilized for the regeneration of alveolar bone, dentin and pulpal complex, or the periodontal regeneration.

**What would happen in the next decade remains to be seen but it is sure that the practice of dentistry will change under the pressure of growing knowledge in medical genetics.**

**Conclusion:**
Molecular genetics identifies the network of genes involved in craniofacial complex development and provide information how mutant genes play a role in disorder causation. So, molecular genetics and molecular dentistry have the potential to shape the dental education and practice. In the context of genetic medicine, the dentist will integrate the tools of genetics in their dental practice for prediction, prevention and personalized therapy.

**References**


**Corresponding author:**
Dragos T. Stefanescu
E-mail: genetics.dentistry@gmail.com
DISCUSSION ON A CASE OF STICKLER SYNDROME

Otilia Marginean¹, Ioan Simedrea¹, Maria Puiu¹, Belei Oana¹, Bochean Camelia², Tamara Marcovici¹, Daniela Chiru¹

¹. Iᵃ Pediatric Clinic, University of Medicine and Pharmacy “Victor Babes” Timisoara, Romania
². Ambulatory Clinic of Emergency Hospital for Children “Louis Turcanu” Timisoara, Romania

Abstract
Stickler syndrome is a connective tissue disorder that can include ocular findings of myopia, cataract and retinal detachment; hearing loss that is both conductive and sensorineural; underdevelopment of the middle part of face, ogival palate, spondylo epiphyseal dysplasia and/or precocious arthritis. The authors present the case of a 7 month infant with ocular findings and specific facial phenotype that was admitted for diagnosis establishment.

Key words: Stickler syndrome, congenital cataract, myopia, conductive and sensorineural hearing loss

Case report
T.V., 7 months old boy, was admitted in hospital in October 2009 for upper respiratory tract infection, but what impressed at this patient was the individual phenotype with facial dysmorphism, microcephaly, congenital cataracts, horizontal nystagmus and mild psycho-motor retardation(Figure 1). The family history of ocular disorders includes two maternal uncles with acquired amblyopia of unknown etiology, one of whom died in a car accident and the other being alive and presenting blindness. (Figure 2)

In the personal history, T.V. is a young couple's first child, from rural areas, T.V. being born at term in cranial presentation, weighing 3250 g, height 49 cm, Apgar score 10, with good neonatal adaptation. He was breastfeeding for a month, then fed with cow's milk and diversified incorrectly at three months. He has been vaccinated only BCG and Engerix in maternity, other vaccinations were not performed by the age of 7 months when he presented in our clinic. In infancy he presented several episodes of upper respiratory tract infections treated at home. Clinical examination upon admission revealed an infant with the following anthropometric indices: weight of 8100 g, high 74 cm, 43 cm cranial perimeter, thoracic perimeter of 47 cm and 45 cm abdominal perimeter. Particular facial phenotype was characterized by underdevelopment of the middle part of face, micrognathia, ogival palate. The infant presented a pronounced horizontal nystagmus. Skin was pale. The pharynx was congested, the baby presented nasal obstruction and rare irritating cough, but normal lung auscultation. It was detected a second degree systolic murmur. The infant showed generalized hypotonia with pronounced tendon reflexes in the legs. The baby maintained its own head, was not sitting alone in the sitting position, not standing alone or with support in standing, and said polysyllabic words. He presented chaotic eye movements, he didn’t follow the examiner face, nor respond to his mimic, he was not following with the eyes moving objects. No other changes were detected in the rest of examination.
Laboratory examinations revealed severe iron deficiency anemia, hypochromic microcytic, hypocalcemia, hypomagnesemia, hipogammaglobulin and moderate hepatic cytolsis. (Table 1)

TORCH serology was negative.

Skull radiography revealed normal thickness cap, suture according to age, turkish saddle according to age.

Echocardiography: aorta = 12.7 mm, opening aorta = 7.14 mm, left atrium = 14.4mm, left ventricle = 16.6 / 23.6 mm, EF = 0.59, FS = 29.79 mm, interatrial septum = 5.18 mm, apparently without defects, right atrium = 17.1 mm, right ventricle = 13.5 mm. The anterior mitral valve prolapse protosistolic with regurgitation. Aortic insufficiency. No fluid in pericardium.


Papillary and photomotor reflexes were present. Oftalmometry = 8 mm

Ophthalmoscopy (Dilated Fundus Exam - DFE): no shine.

Neurologic exam: muscular hypotonia, horizontal nystagmus; opsoclonus; psychomotor retardation with stereotypy.

Electroencephalogram (EEG Test): theta-delta rhythm, with many artifacts.

Ear, nose and throat (ENT) examination: normal eardrums colored, well viewed items.


Papillary and photomotor reflexes were present. Oftalmometry = 8 mm

Ophthalmoscopy (Dilated Fundus Exam - DFE): no shine.

Taking into consideration clinical and laboratory criteria: ophthalmic, otic, cardiac and cranio-facial changes and the karyotype, we can sustain the diagnosis of Stickler syndrome.

During hospitalization in our clinic, the infant presented several episodes of watery diarrhea, possibly of viral etiology, which resolved under medical and dietary treatment (lactose-free milk, Colimicina, Smecta) without dehydration syndrome and electrolyte disorders. Pale skin was associated with pronounced low values of hemoglobin and the number of red blood cells, which required red blood cells transfusion. The treatment for upper respiratory tract infection was performed with acetaminophen syrup orally and 1% ephedrinated serum intra-nasal. For muscle hypotonia we initiated the therapy with Cerebrolizyn, which was well tolerated. For transient hepatocytolitic syndrome accompanying probably diarrhea, the infant received intravenous infusion of Arginine and Aspatofort and transaminases return to normal in 14 days. Roborant treatment given to infant was consisted from group B vitamins (B1, B6, C) and gluconic calcium 10% in slow iv injection.
Discussions – Stickler Syndrome

Stickler syndrome is a genetic disorder with autosomal dominant transmission. Mutations affecting one of three genes: COL2A1, COL11A1, COL11A2 have been associated with disease. Because a small number of families with Stickler syndrome features showed no mutations in these three mentioned genes, it appeared the hypothesis of mutations occurred at the level of other genes. Given the autosomal dominant mode of transmission of the disease, affected patients shows a 50% risk of transmitting the mutant gene to each of successors. Because of the wide clinical variability of the disease that can occur within the same family, it must be assessed the relative risk of developing the disease and providing genetic counseling, like in the case of infant T.V. (Figure 2)

Diagnosis

Clinical diagnosis criteria have not yet been established for Stickler syndrome. It should be noted in subjects who have two or more of these categories of diseases: (2,3,4,5,6)

1. Ophthalmologic criteria: congenital cataract or early onset in infancy, myopia greater than -3 diopters, abnormal vitreous, retinal detachment. Usually, babies are farsighted (1 diopter or more), so the discovery of a degree of myopia in risk newborn (with Pierre-Robin phenotype or with a parent affected) is suggestive for the diagnosis of Stickler syndrome. In the disease were observed two types of vitreous abnormalities. Type I, which is most commonly seen, consists of a persistent vestigial vitreous gel in the retrolental space, bounded by a membrane. Type II, more rare, is characterized by the presence of bands thickened, irregular, dispersed into the vitreous cavity. In our case, the baby T.V. shows the phenotype Pierre-Robin described above, and ocular changes: microphthalmia, corneal decreased in size in horizontal and vertical axis, and crystalline opacities, subcapsular above, white color.

2. Ear criteria: hearing loss, conductive or sensorineural. The degree of hearing damage is variable and can grow progressively. Approximately in 40% of the studied cases it has been described sensorineural deafness typically with loss of hearing for high tones.
<table>
<thead>
<tr>
<th>Date</th>
<th>Hemoglobin</th>
<th>RBC</th>
<th>WBC</th>
<th>Platelet</th>
<th>Inflammation</th>
<th>Electrolytes</th>
<th>ABG</th>
<th>Protein levels</th>
<th>LDH</th>
<th>Hepatic</th>
<th>Renal</th>
<th>Glucose</th>
<th>Microscopic examination of urinary sediment</th>
<th>Stool parasitology test</th>
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<td>6.8 g/dl</td>
<td>1.87x10⁶/µL</td>
<td>6.6x10⁷/µL</td>
<td>175.000 / µL</td>
<td>ESR=6mm/h</td>
<td>Na=134, K=3.99, Ca=2.2, Cl=98, Mg=0.76 mmol/l</td>
<td>pH = 7.34, pCO2 = 17.6mmHg</td>
<td>60 g/l; A = 66.7%, α₁=3.2%, α₂ = 10.4%, β = 10.8%, γ = 8.9%</td>
<td>820 U/L</td>
<td>GPT = 55U/l</td>
<td>BUN = 6.87mmol/l</td>
<td>3.5 mmol/l</td>
<td>Albuminuria absent, 1-3 WBC per high power field, rare hyaline cylinders, rare epithelial cells</td>
<td>NEGATIVE</td>
<td>NEGATIVE</td>
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<td>23.10.2003</td>
<td>10.2 g/dl</td>
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<td>8.8x10⁷/µL</td>
<td>220.000 / µL</td>
<td>CRP: negative</td>
<td>Na=138, K=4.33, Cl=104 mmol/l</td>
<td>BE = -9.6mmol/l</td>
<td>64.6g/l</td>
<td></td>
<td>GPT = 71U/l</td>
<td>GOT = 73U/l</td>
<td></td>
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<td>01.11.2003</td>
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<td>4.0x10⁶/µL</td>
<td></td>
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<td></td>
<td>GPT = 16 U/l</td>
<td>GOT = 12 U/l</td>
<td></td>
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Table 1. Laboratory datas of T.V
The exact mechanism is unclear and has been linked to the expression of collagen type II and IX in the inner ear. In type I Stickler syndrome, sensorineural hearing impairment is mild and with no progressive evolution, and is less severe compared with the audiological degradation in types II and III Stickler syndrome. Conductive deafness occurred in some cases may be secondary to recurrent ear infections favored by ogival vault, and/or secondary to a defect of the middle ear ossicles.

Infant audiometry performed to T.V. infant showed mixed hearing loss, conductive and sensorineural.

3. Craniofacial changes: hypoplasia of the middle part of the face, deepened nose base, sharp nose, with nostrils anteversion, long filter, uvula bifida, ogival palate, micrognathya, Pierre Robin phenotype (micrognathya, ogival arch, glossoptosis). Flat facial profile, caused by underdeveloped jaw and nose base, can cause telecanthus and epicanthus folds. Hypoplasia of the middle face is more pronounced in infants and young children, some subjects may have a normal facial profile. T.V. baby facies is characteristic for Pierre-Robin phenotype, involving extra microcephaly.

4. Articular changes: Skeletal manifestations consist of early-onset osteoarthritis, hypermobility (joint laxity), short stature and radiographic changes of medium spondylo-epiphysis dysplasia. Some individuals may have “marfanoid” features, but with no tall stature. Joint laxity can be found in children and become less important with age. Stickler syndrome common spinal abnormalities (scoliosis, kyphosis) can lead to chronic back pain.

In our presented case no skeletal changes were detected on admission.

5. Cardiac changes: association with mitral valve prolapse was reported in 50% of the cases studied in a clinical trial and in a much smaller proportion of cases in another series, which is present in T.V. infant.

According to recent studies, not all criteria are needed to comply with Stickler syndrome.

Figure 3. Genetic tree of T.V.
Genetics

Stickler syndrome is a genetic disorder with autosomal dominant transmission. Mutations produced in the following three genes were associated with the appearance of type I, II and III Stickler syndrome: COL2A1 (chromosome 12, 12q13.11-q13.2 locus), COL11A1 (chromosome 1, 1p21 locus), COL11A2 (chromosome 6, 6p21.3 locus). (Table 2)

In some families with characteristic clinical changes of Stickler syndrome were not uncovered any one of these three mutations mentioned. It has been hypothesized the existence of mutations in other genes, still unidentified, present also in this disease.

Most patients diagnosed with Stickler syndrome presents the type I of the disease, with mutations in COL2A1 gene, while mutations in the gene COL11A1 (type II) were only recently described. Lately, in a few cases have been described also mutations in COL11A2 gene that causes Stickler syndrome type II, where all eye changes are missing.

Normal product of the COL2A1 gene activity is represented by chains of type II collagen, a major structural component of cartilage tissue. Mutations in this gene cause the premature termination of translation and consequently reduces type II collagen synthesis. COL11A1 gene encode an α chain synthesis of collagen type XI, which is supposed to play an important role in collagen fibrils genesis, controlling the lateral growth of collagen II fibrils. COL11A1 gene mutations alter the synthesis and function of collagen type XI.

COL11A2 gene encode α 2 chain synthesis of collagen type XI, expressed in cartilage, but not at the level of liver, skin and tendons. COL11A2 gene mutations also cause abnormal synthesis of collagen XI.

In the COL2A1 gene appears a premature stop mutation that causes failure of the normal gene product synthesis, type II collagen. Most patients shows the type I vitreous anomaly and are at increased risk of retinal detachment, do not present hearing impaired or have a mild form of sensorineural deafness and shows early arthritis, and craniofacial changes are variable. COL11A1 gene mutation was observed in patients with typical phenotype of Stickler syndrome. Usually these patients have a more severe hearing impairment and type II congenital vitreous anomaly.

Gene mutation in COL11A2 cause Stickler syndrome without eye changes. (7, 8, 9, 10, 11, 12)

Clinical examination, biological investigations, laboratory and karyotype, performed in conjunction with interdisciplinary exams excluded a number of related genetic disorders. Karyotype case presented describes mutation in the gene COL11A1 - locus 1p21 (46 XY, 1qh +, 21s +, yq +; chromosomal heteromorphysm with elongation of secondary constriction of chromosome 1, increase satellites on chromosome 21, and heteromorphysm of the Y chromosome), so make part of Stickler syndrome type II.

<table>
<thead>
<tr>
<th>Type of disease</th>
<th>Mutant gene</th>
<th>Mutant locus</th>
<th>Synthesis product of the gene</th>
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<td>Stickler syndrome type I</td>
<td>COL2A1</td>
<td>12q13.11-q13.2</td>
<td>α1 chain of type II collagen</td>
</tr>
<tr>
<td>Stickler syndrome type II</td>
<td>COL11A1</td>
<td>1p21</td>
<td>α1 chain of type XI collagen</td>
</tr>
<tr>
<td>Stickler syndrome type III</td>
<td>COL11A2</td>
<td>6p21.3</td>
<td>α2 chain of type XI collagen</td>
</tr>
</tbody>
</table>

Table 2. The appearance of type of Stickler syndrome
Diseases that show phenotypes associated with COL2A1 and COL11A2 gene mutations were excluded, in our case it is not the type I or III Stickler syndrome according to karyotype.

1. Phenotypes associated with mutations in COL2A1 gene:
   - Achondrogenesis type II: characterized by virtual absence of ossification of the spine, sacrum and bin, with the consequent appearance of shortening of the trunk and limbs, with prominent abdomen and dropsical issue. Death occurs in utero or in early neonatal period.
   - Hypochondrogenesis - term used for describing a medium form of achondrogenesis.
   - Congenital spondylo-epiphyseal dysplasia: although skeletal changes are similar to those described in Stickler syndrome, these are more severe and cause significant short stature. In addition, affected subjects may present flat profile, myopia or vitreous and retinal degeneration.
   - Kneist dysplasia: affected subjects may present disproportionate short stature, flat facial profile, myopia, vitreous and retinal degeneration, ogival palate, kyphosis scoliosis, and multiple radiological spinal changes.
   - Early-onset arthropathy: the disease is transmitted autosomal dominant, in 1990 being identified the COL2A1 gene mutation incriminated in the disease - the substitution of arginine to cysteine in position 519 of the α1 chain of type II collagen.

2. Phenotypes associated with mutations in COL11A2 gene:
   - Autosomal recessive spondylo-metaepiphyseal dysplasia: the disease is characterized by flat facial profile, sharp hard palate and severe deafness. Recently it has been hypothesized that type III Stickler syndrome - a form without eye changes could be considered a type of the disease.

   - Weissenbach-Zweymuller syndrome (WZS) was described as “neonatal Stickler syndrome”, but now is a distinct entity, characterized by hypoplasia of the middle part of face, clogged nose and top with the sharp nose, micrognathya, sensorineural hearing loss and limb shortening. Radiological changes include the femur and humerus in the form of "weightlifting". Skeletal changes are less obvious in their lives and resume growth after 2-3 years of life is common.

   - Non-syndromic sensorineural deafness: in 1999 were described mutations in the COL11A2 gene in two unrelated families suffering from non-syndromic nonprogressive deafness.

3. Stickler syndrome type II described in infants T.V. must be differentiated from other similar genetic diseases related to phenotype, who also associated mutations in the gene COL11A1:
   - Marshall syndrome: Affected individuals shows hypertelorism, maxillary hypoplasia and hypoplasia of the nasal bones, clogged nose and the nasal tip pointed. Unlike Stickler syndrome, flat facial profile is more evident in adults. Impaired eyes include: myopia, vitreous humor fluid and early onset cataracts. Sensorineural hearing loss is common and may progress. Nanism and early arthritis may occur. Skin manifestations are also described - hipotricosis and hipohidrosis. T.V. baby does not have early cataracts, skin manifestations or early onset arthritis, but the differential diagnosis remains questionable, taking into consideration the opinions of some authors which categorizes Marshall syndrome as a variant of Stickler syndrome II. (13, 14, 15, 16, 27, 18, 19, 20)
Conclusions
1. Stickler syndrome is under diagnosed.
2. Medical family history, clinical exams and karyotype are necessary for diagnosis.
3. Given the model of autosomal dominant genetic transmission, providing genetic counseling is needed in this case.

References
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Corresponding author:
Dr. Tamara Marcovici,
C4 Mihail Kogalniceanu Street,
300133, Timisoara, Romania;
Phone: 0723694950;
E-mail: t_marcovici@yahoo.com
ACHONDROPLASIA – CASE PRESENTATION

Dana Metea¹, Andreea Mazilu¹, Adelina Timofte², Maria Puiu¹, David VL³

¹. University of Medicine and Pharmacy “Victor Babes” Timisoara, Romania
². Municipal Hospital Timisoara, Romania
³. Emergency Children’s Hospital “Louis Turcanu” Timisoara, Romania

Abstract
Achondroplasia is a skeletal dysplasia caused by a mutation in fibroblast growth factor receptor 3 gene (FGFR3) on chromosome 4p. We present you case of a 4 months old female with achondroplasia admitted in our clinic. We present you the pathway to the diagnostic, the treatment options, the outcomes and the particularities of this case.

Key words: genetic disorders, systemic lupus erythematosus

Background
Achondroplasia is a skeletal dysplasia with extreme, disproportionate, short stature. It is the most common non-lethal skeletal dysplasia. Its incidence is between one in 10,000 and one in 30,000. The phenotype is characterized by rhizomelic disproportionate short stature, enlarged head, midface hypoplasia, short hands and lordotic lumbar spine, associated with normal cognitive development. This autosomal-dominant disorder is caused by a mutation in fibroblast growth factor receptor 3 gene (FGFR3) on chromosome 4p.

Case presentation: A 4 months old girl was admitted in our clinic with the suspicion of hydrocephalus because of her large head. Birth history: GI PI, born at 40 weeks gestational age, 2900 g, 7 APGAR score, difficult neonatal adaptation, moderate respiratory distress, difficult breast feeding, hypertonia. Vaccination on schedule.

Clinical examination revealed a short stature infant with 5.6 kg weight, somatometric indices below the national values: height=55 cm (67,3 +/- 2,85), chest circumference=35 cm (40,92 +/- 2,25); head circumference=44,5 (34,3 +/- 1,30) 70 cm, pale, abnormal body proportion: short arms and legs, normal torso size (Fig. 1). Reduced height, upper arms/thighs more shortened than forearms/lower legs, limited elbow extension, bowlegs.

Fig. 1. General abnormal aspect of the child
Large head with frontal bossing, hypoplasia of the midface, flat nose, low implanted ears (Fig. 2), stubby fingers, „trident” hand (separation between middle and ring fingers), scoliosis, decreased muscle tone, anterior fontanel=4/4 cm, normotensive, slightly motor retardation. X-ray revealed rhizomelic shortening of the bilateral femurs with metaphyseal flaring rhizomelic shortening of the humerus (Fig. 2 and 3). Laboratory investigations: normal values (including TSH, FT4 and ELISA Toxo). Abdominal and cardiac ultrasound: normal. EEG: normal for the age of 4 months. Cariotype: normal. Transfontanelar Ultrasound – anterior coronary section: enlargement of the frontal interemisferic space, normal appearance of lateral ventricles, normal thalamus and caudate nucleii (Fig. 4). CT of the head CT revealed pronounced frontal cortical atrophy (Fig. 5).

For differential diagnosis many conditions have been considered as follow:
1. Thanatophoric dwarfism: short-limbed dysplasia, large head, short neck, narrow thorax, short and small fingers, and bowed extremities. This condition is lethal in the neonatal period
2. Pseudoachondroplastic dysplasia in most of the cases, is not diagnosed until 2-3 years of age, since growth is normal at first. Usually first detected by a delay in crawling, walking, or a curious, waddling gait.
3. Achondrogenesis characterized by very short stature (≤ 35 cm), arms, legs and neck, usually born prematurely, stillborn, or die shortly after birth from respiratory failure (Ellis van Creveld syndrome)
5. Chondrodysplasia punctata (Conradi disease): typical X-ray/ Long bones stippled epiphyses, short femur deformity
6. Hypothyroid dwarfism associates stunted body growth and mental development appearing in the first years of life, abnormal TSH and FT4

Fig. 2. Large head with frontal bossing, hypoplasia of the midface, flat nose

Fig. 3. Image shows rhizomelic shortening of the bilateral femurs with metaphyseal flaring
Complications
Morbidity associated with achondroplasia may include the following: Recurrent otitis media, neurologic complications due to cervicomedullary compression (hypotonia, respiratory insufficiency, apnea, cyanotic episodes, feeding problems, quadriplegia, sudden death), cardiovascular complications obstructive and restrictive respiratory complications (upper airway obstruction, pneumonia, sleep apnea), hydrocephalus, spinal deformities (kyphosis, lordosis, scoliosis), obesity, spinal canal stenosis, genu varum, behaviour disorders.

Treatment
There is no specific treatment for this condition. Growth hormone can be used to augment the height of patients with achondroplasia. However, no long-term studies exist to determine final height, nor do any randomized controlled studies exist to justify prolonged treatment with growth hormone in patients with short stature. Surgical treatment to solve complications like: spinal canal stenosis, thoracolumbar kyphosis, genu varum, foramen magnum decompression (neurosurgery), limb lengthening.

Follow-up
This child needs interdisciplinary clinical and biological monitoring: orthodontist, speech therapist, otolaryngologist, geneticist, pulmonologist, pediatrician, orthopedics specialist every 3 months during childhood.

Particularity of the case
The presence of pronounced frontal cortical atrophy which may lead to serious problems of neuropsychic development of this child; in the absence of a family history and considering the advanced age of his parents we can establish that the etiology of the condition is a result of a de novo mutation.

References

**Corresponding author:**
Adelina Timofte
Sirius Street no7, ap7
Timisoara
e-mail: albastru_amb@yahoo.com
OBESITY IN RARE DISEASES AND GENETIC FACTORS IN THE “FREQUENT” CHILDHOOD OBESITY

Chirita Emandi Adela¹; Puiu Maria²; Micle Ioana¹

¹. Emergency Children’s Hospital “Louis Turcanu” Timisoara-Department of Diabetes, Nutrition and Metabolic Diseases
². University of Medicine and Pharmacy “Victor Babes” Tmisoara, Romania

Abstract

Context: In order to create the best management schemes and determine novel therapeutic targets, it is essential to understand the factors causing today’s rising epidemic of childhood obesity. This article provides an overview of the current knowledge on monogenic and syndromic forms of obesity, and the genetic contribution to complex polygenic obesity - “frequent” childhood obesity - that is caused by the interaction between multiple genes and the environment.

Evidence Acquisition: Published literature (free full text), addressing genetic factors associated with common obesity and current knowledge of genetics of monogenic and syndromic forms obesity was analyzed. Evidence Synthesis: Neuroendocrine mechanisms of appetite regulation are the main concerns of the current genetic evidence in obesity. Monogenic forms of disease explain 5% of children with extreme obesity, having hyperphagia associated with defects in the leptin-melanocortin pathway, as a central feature. Candidate gene association studies indicate that more subtle variations of the same genes also contribute to common forms of obesity. Well-powered genome-wide association studies identified ‘fat mass and obesity associated’ gene (FTO) as a strong contributor to childhood obesity, providing new insights into pathogenic mechanisms of a common complex disease.

Conclusions: Although there has been some very important recent progress in elucidating genetic mechanisms underlying obesity, we are still a long way from explaining the high heritability of adiposity. For the clinician it is important to identify particular phenotypes and clinical features that can help to recognize the children who need genetic screening.

Key words: child, obesity, genetic

Context

Worldwide, we are confronted with a rising prevalence of childhood obesity that has reached epidemic proportions. Intense efforts are being made to identify the causes, in order to address them specifically in treatment management.

Considering the genetic point of view, obesity is classified in:

1. **monogenic obesity**, that is the obesity associated with a single gene mutation; in these cases single gene variants are sufficient by themselves to cause obesity in food abundant societies; patients with monogenic obesity usually show extremely severe phenotypes characterized by childhood obesity onset, often associated with additional behavioral, developmental or endocrine disorders;

2. **syndromic obesity** includes some Mendelian disorders in which patients are clinically obese and are additionally distinguished by mental retardation, dysmorphic features, and organ-specific developmental abnormalities;

3. **polygenic obesity**, the very common kind of obesity, which concerns the great majority of obese children, arises when an individual genetic make-up is susceptible to an environment that promotes energy consumption over energy expenditure;
Evidence synthesis

1. Monogenic obesity

Genetic disruption of the leptin–melanocortin pathway results in monogenic human obesity

Energy homeostasis involves the integration of afferent signals from fat (leptin) and pancreatic β cells (insulin) and meal-related afferent signals from the gut. These inputs are integrated within the brain and regulate food intake, energy expenditure, energy partitioning and neuroendocrine status.

The adipocyte-derived hormone leptin circulates in proportion to body fat content, crosses the blood–brain barrier, and stimulates a subset of neurons in the hypothalamus that produce peptides that reduce feeding and promote increased energy expenditure (leptin–melanocortin pathway). Leptin inhibits hypothalamic neurons that produce peptides promoting feeding and decreased energy expenditure.

Attention has focused on identifying the molecular events that lie downstream of the leptin receptor in hypothalamic target neurons. In particular, neurons within the hypothalamus act as primary sensors of alterations in energy stores to control appetite and energy homeostasis. Pro-opiomelanocortin (POMC) neurons produce the anorectic peptide α-MSH (α-melanocyte stimulating hormone) together with CART (cocaine- and amphetamine-related transcript), whilst a separate group expresses the orexigens: neuropeptide Y (NPY) and agouti-related protein (AGRP). AGRP is a hypothalamic neuropeptide that is a potent melanocortin-3 receptor (MC3R) and melanocortin-4 receptor (MC4R) antagonist. Activation of the NPY/AGRP neurons increases food intake and decreases energy expenditure, whereas activation of the POMC neurons decreases food intake and increases energy expenditure (1)

The cumulative prevalence of monogenic obesity among children with severe obesity is about 5%.

Several monogenic disorders resulting from disruption of the leptin–melanocortin pathway have been identified. In these disorders, severe obesity of early onset is itself the predominant presenting feature, although often accompanied by characteristic patterns of neuroendocrine dysfunction.

Congenital leptin deficiency

In 1997 two severely obese cousins were reported from a highly consanguineous family of Pakistani origin (2). Despite their severe obesity, both children had undetectable levels of serum leptin and a mutation in the gene encoding leptin. Leptin deficiency is associated with hyperphagia and increased energy intake. Other phenotypic features include hypogonadotropic hypogonadism, elevated plasma insulin, T-cell abnormalities, and advanced bone age.

The role of leptin in some monogenic forms of obesity was further supported by the striking effect of leptin replacement in an extremely obese child with congenital leptin deficiency. In a 9 year old boy with congenital leptin deficiency, daily subcutaneous injection of recombinant human leptin for a year led to a complete reversal of obesity, with sustained fat-mass loss. Moreover, partial leptin deficiency in 13 Pakistani subjects, owing to a heterozygous frameshift mutation in the leptin gene, was found to be associated with increased body fat. (3,4) However, only a handful of families with extreme forms of obesity in early infancy have mutations in these genes (5).

Mutation in the leptin receptor

Shortly after leptin deficiency was discovered, a similar phenotype, but with elevated plasma leptin levels, was identified. It was caused by a homozygous mutation in the leptin receptor. A later study suggested that approximately 3% of severe morbid obesity in a population including both nonconsanguineous and consanguineous families could be explained by mutations in the leptin receptor (6).
<table>
<thead>
<tr>
<th>History</th>
<th>Suggested Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early onset (!!! 5 years of age)</td>
<td>genetic disorders</td>
</tr>
<tr>
<td>Visual impairment and deafness</td>
<td>genetic disorders</td>
</tr>
<tr>
<td>Primary hypogonadotropic hypogonadism or hypogenitalism</td>
<td>genetic disorders</td>
</tr>
<tr>
<td>Family history: consanguineous relationships, other children affected</td>
<td>genetic disorders</td>
</tr>
<tr>
<td>Hyperphagia—often denied, ask specific questions such as waking at night to eat, demanding food very soon after a meal</td>
<td>if severe, suggests a genetic cause for obesity</td>
</tr>
<tr>
<td>Mood disturbance and central obesity</td>
<td>Cushing’s syndrome</td>
</tr>
<tr>
<td>Frequent infections and fatigue</td>
<td>ACTH deficiency due to POMC mutations</td>
</tr>
<tr>
<td>Dry skin, constipation, intolerance to cold fatigue</td>
<td>hypothyroidism</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>behavioral disorders</td>
</tr>
<tr>
<td>Short duration of obesity</td>
<td>endocrine or central cause</td>
</tr>
<tr>
<td>Onset and tempo of pubertal development</td>
<td>endocrine disorders</td>
</tr>
<tr>
<td>Damage to the CNS (e.g. infection, trauma, hemorrhage, radiation therapy, seizures)</td>
<td>hypothalamic obesity, pituitary GH deficiency or pituitary hypothyroidism</td>
</tr>
<tr>
<td>Morning headaches, vomiting, visual disturbances, excessive urination or drinking</td>
<td>tumor or mass in the hypothalamus</td>
</tr>
<tr>
<td>Treatment with certain drugs or medications</td>
<td>obesity related to drugs</td>
</tr>
</tbody>
</table>

**Examination**

<table>
<thead>
<tr>
<th>Investigated Feature</th>
<th>Suggested Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysmorphic features or skeletal dysplasia</td>
<td>genetic disorders</td>
</tr>
<tr>
<td>Red hair (if not familial)</td>
<td>mutations in POMC in white Caucasians</td>
</tr>
<tr>
<td>Tall stature (on the upper centiles)</td>
<td>common obesity, but also MC4R deficiency</td>
</tr>
<tr>
<td>Selective fat deposition (60%)</td>
<td>leptin and leptin receptor deficiency</td>
</tr>
<tr>
<td>Short stature or a reduced rate of linear growth</td>
<td>GH deficiency, hypothyroidism, cortisol excess, pseudohypoparathyroidism, or a genetic syndrome</td>
</tr>
<tr>
<td>Central body fat distribution with purple striae</td>
<td>Cushing’s syndrome</td>
</tr>
<tr>
<td>Diminished growth rate and pubertal development</td>
<td>growth hormone deficiency, hypothyroidism, cortisol excess, and genetic syndromes</td>
</tr>
<tr>
<td>Accelerated growth rate and pubertal development</td>
<td>precocious puberty and some girls with PCOS</td>
</tr>
<tr>
<td>Acanthosis nigricans</td>
<td>insulin resistance</td>
</tr>
</tbody>
</table>

**Investigations**

- Fasting and 2-hour glucose and insulin levels
- Proinsulin if PC-1 deficiency considered
- Fasting lipid panel
- Thyroid function tests
- Serum leptin
- Karyotype, DNA for molecular diagnosis
- Bone age, Growth hormone (GH) secretion and function tests, when indicated
- Assessment of reproductive hormones, when indicated
- Serum calcium, phosphorus, and parathyroid hormone levels to evaluate for suspected pseudohypoparathyroidism
- MRI scan of the brain with focus on the hypothalamus and pituitary
- ACTH, adrenocorticotropic hormone;
- POMC, pro-opiomelanocortin; MAOI, monoamine oxidase inhibitor; MC4R, melanocortin-4 receptor; PC-1, prohormone convertase-1.

Table 1. Assessment of the obese child
POMC deficiency
Small numbers of patients have been described with mutations in the gene encoding pro-opiomelanocortin (POMC), which is involved in the leptin-melanocortin pathway. (7,8) Initial presentation is, in neonatal life, with adrenal crisis due to ACTH deficiency (POMC is a precursor of ACTH in the pituitary) and the children have pale skin and red hair due to the lack of MSH action at melanocortin-1 receptors in the skin and hair follicles. POMC deficiency results in hyperphagia and early-onset obesity due to loss of melanocortin signaling at the melanocortin-4 receptor (MC4R).

Prohormone convertase-1 (PC1) deficiency
Jackson et al described a woman with severe early-onset obesity, hypogonadotropic hypogonadism, postprandial hypoglycaemia, hypocortisolaemia, and evidence of impaired processing of POMC and proinsulin who was a compound heterozygote for PC1 mutations.(8)

Melanocortin-4 receptor deficiency
Mutations in another component of the leptin–melanocortin pathway melanocortin-4 receptor (MC4R) have also been associated with obesity. MC4R deficiency represents the most common monogenic obesity disorder that has been identified so far. It is present in about 5-6% of obese individuals from different ethnic groups, with a higher prevalence in cases with increased severity and earlier age of onset. (9,10) Affected subjects exhibit hyperphagia, but this is not as severe as that seen in leptin deficiency, although it often starts in the first year of life. Alongside the increase in fat mass, MC4R-deficient subjects also have an increase in lean mass that is not seen in leptin deficiency and a marked increase in bone mineral density; thus they often appear ‘big-boned’. The accelerated linear growth does not appear to be due to dysfunction of the GH axis and may be a consequence of the disproportionate early hyperinsulinaemia. Interestingly, both heterozygous and homozygous mutations in MC4R have been implicated in obesity, but extreme obesity is incompletely penetrant in heterozygous patients. In other words, some individuals with a single copy of the mutation are obese, whereas others are not obese. While at present there is no specific therapy for MC4R deficiency, it is highly likely that these subjects would respond well to pharmacotherapy that overcame the reduction in the hypothalamic melanocortinergic tone that exists in these patients.(11)

Studies of patients with early-onset severe obesity have revealed the identity of very few genes associated with obesity. Furthermore, the few gene mutations associated with morbid obesity appear to influence body weight primarily by altering appetite. Although some of the molecules may also impact activity, this has not yet been shown to be a significant contributor to obesity. A significant limitation of the strategy of focusing on morbid obesity is that mutations or genetic variants in these genes may not be associated with more common forms of the condition.

2. Syndromic obesity
Syndromic obesity is represented by at least 20 rare syndromes that are caused by discrete genetic defects or chromosomal abnormalities, both autosomal and X-linked, that are characterized by obesity. Most of these obesity syndromes are distinguished by the presence of mental retardation. It was expected that the syndromic forms of obesity could help to unravel novel genes relevant for idiopathic obesity. However, although the genes for several of the syndromic forms have been detected, the relevance of these genes for general obesity is still unclear. (12,13)

Prader–Willi syndrome
The most frequent of these syndromes (1 in 25,000 births) is Prader–Willi syndrome (PWS), an autosomal-dominant disorder, characterized by obesity, hyperphagia, muscular hypotonia, mental retardation, short stature and hypogonadotropic
hypogonadism. It is usually caused by a paternally inherited deletion at the chromosomal region 15q11.2–q12, and less frequently by maternal uniparental disomy. The cause of hyperphagia in PWS remains elusive, although PWS phenotypes are consistent with a combined hypothalamic impairment, causing several endocrine abnormalities. It was also suggested that the elevated production of the stomach secreted peptide ghrelin seen in PWS might increase appetite by interacting with the POMC/CART and NPY hypothalamic neurons.

**Sim-1**
The loss of the single minded homologue 1 (SIM1) gene has also been associated with hyperphagia in syndromic obesity. This gene encodes a transcription factor that has a pivotal role in neurogenesis. In humans, deletion or disruption of the SIM1 region results in either a ‘Prader–Willi-like’ phenotype or a form of early-onset obesity that is associated with excessive food intake.

**WAGR**
The WAGR syndrome (Wilms tumour, anorexia, ambiguous genitalia, mental retardation and obesity) is one of the best-studied contiguous gene syndromes associated with chromosomal deletions at 11p13, the location of the WT1 gene.

**Pseudohypoparathyroidism type 1A (PHP1A)**
PHP1A syndrome is due to a maternally transmitted mutation in GNAS1, which encodes the α-subunit of the Gs protein. Food-intake abnormalities in patients with this syndrome might be due to the expression of the resulting variant Gs protein in the hypothalamic circuitry that controls energy balance, which involves many G-protein coupled receptors.

**Bardet–Biedl syndrome (BBS)**
The origin of obesity is more complex in Bardet–Biedl syndrome (BBS), which is characterized by six main features: Rod-Cone Dystrophy (the most frequent phenotype), polydactyly, learning disabilities, hypogonadism in males, renal abnormalities and obesity. In BBS patients, obesity has early onset, usually arising within the first few years of life. However, one study of post-pubertal BBS patients found that only 52% were clinically obese; therefore, this syndrome can present with a heterogeneous phenotype.

**Albright’s hereditary osteodystrophy**
Albright’s hereditary osteodystrophy (AHO) is an autosomal dominant disorder due to germline mutations in GNAS1 which encodes for α-subunit of the stimulatory G protein (Gsa).

**Fragile X syndrome**
Fragile X syndrome is characterized by moderate to severe mental retardation, macroorchidism, large ears, macrocephaly, prominent jaw (mandibular prognathism), high-pitched jocular speech and obesity.

**Borjeson–Forssman–Lehmann syndrome**
Borjeson, Forssman and Lehmann described a syndrome characterized by moderate to severe mental retardation, epilepsy, hypogonadism, and obesity with marked gynaecomastia. Mutations in a novel, widely expressed zinc-finger gene plant homeodomain (PHD)-like finger (PHF6) have been identified in affected families, although the functional properties of this protein remain unclear.

**Alstrom syndrome**
Alstrom syndrome is a homogeneous autosomal recessive disorder that is characterized by childhood obesity associated with hyperinsulinaemia, chronic hyperglycaemia and neurosensory deficits. Subsets of affected individuals present with additional features such as dilated cardiomyopathy, hepatic dysfunction, hypothyroidism, male hypogonadism, short stature and mild to moderate developmental delay. Mutations in a single gene, ALMS1, have been
found to be responsible for all cases of Alstrom syndrome. (Orphanet)

3. Complex polygenic obesity
Complex polygenic obesity arises as a result of behavioral, environmental, and genetic factors which may influence individual responses to diet and physical activity. Changes in our environment over the last decades, in particular the unlimited supply of convenient, highly palatable, energy-dense foods; plus a sedentary lifestyle, the so-called “obesogenic” environment coupled with a genetic susceptibility are culprits for today’s obesity epidemic. (17)

Compared with obesity syndromes or single-gene obesity, the recent rapid increase in prevalence of childhood obesity suggests that environmental factors probably have a larger influence on body weight in typical obesity patients, although individual responses to these environmental factors are influenced by genetic factors (’susceptibility genes’). Heritability is the proportion of phenotypic variance that is due to genetic effects. Traditionally the most frequently used model for separation of the genetic component of variance is based on studies of twins. Overall, data from twin and adoption studies show that different individuals have a certain genetic predisposition to store excessive caloric intake as fat. Different sets of twins showed remarkable differences in the degree to which these calories were stored as fat, but the tendency toward increased adiposity within each set of twins was remarkably similar, indicating that genetic factors determine an individual’s susceptibility to gain weight in a given environment. (18,19) Twin studies showed a heritability of around 0.7 for BMI in adults and children, and comparable levels for other measures of adiposity: skinfold thickness, waist circumference, and total and regional fat distribution. This means that around 70% of the individual variation in adiposity between people is apparently due to genetic factors. People at high genetic risk for obesity are more susceptible to the effects of an unhealthy environment. (18,20,21,22,23)

As with other complex diseases, a large number of candidate gene association studies, of variable power, have been performed in obesity and related phenotypes. By far the most strongly replicated candidate gene from these analyses is melanocortin 4 receptor, but other replicated associations include those with adipokine and adipokine receptor genes. Underlining the central role of behavioral stimuli in obesity, alleles of genes encoding dopamine, serotonin, and cannabinoid receptors (DRD2, HTR2C, and CBI) (24,25,26) are also reported to be associated with feeding behavior and related traits. Genome-wide association (GWA) studies have led to the identification of new candidate genes in various disorders, including type 2 diabetes and obesity and a new gene for obesity, ‘fat mass and obesity associated’ gene (FTO). The contribution of the FTO variant is fairly modest, with adult homozygotes for the risk allele having only a 2- to 3-kg increase in weight (27), but the obesity high-risk allele is common in Caucasian populations. Its effects begin early in life. Higher fat mass is observable from the age of 2 weeks, and carriage of the allele is associated with higher BMI and reduced satiety in children. (28,29)

Alternatively, the missing heritability may be accounted for by other genetic factors like genomic copy number variation and epigenetic modifications.

Assessment of the obese child
In order to establish the diagnosis of overweight or obese in a patient, the clinician must evaluate the BMI and compare it to the standardized nomogram, appropriate for the age and sex of the child. According to World Health Organization the definition of overweight and obesity in children is established at the following cut-offs: Overweight: >+1 Standard Deviations (equivalent to BMI 25 kg/m² at 19 years) Obesity: >+2 Standard Deviations (equivalent to BMI 30 kg/m² at 19 years).
The cumulative prevalence of monogenic obesity among children with severe obesity is about 5%. Nevertheless, considering the great proportion of obese children worldwide, the possibility exists that many thousands of children might be carriers of this kind of mutations. There are a lot of genes implicated in obesity and too many obese patients in the world to perform molecular study for everyone. It would be useful to identify particular phenotypes and clinical features that can help to recognize the subjects needing genetic screening (table 1). The presence of severe obesity in a young child (<5 yr old) associated to extreme hyperphagia, severe insulin resistance disproportionate for the degree of obesity and a positive family history of early-onset obesity may support a genetic analysis.

**Conclusion**
All of the genes currently known to cause monogenic or syndromic obesity are expressed in the brain and appear to exert their effects by modulation of feeding behavior. Efforts to identify genetic factors in obesity have yielded some notable successes, but we are still a long way from explaining the high heritability of the condition. From a practical, clinical point of view, it is important to identify particular phenotypes and clinical features that can help to recognize the children who need genetic screening. The presence of severe obesity in a young child (<5 yr old) associated to extreme hyperphagia, severe insulin resistance disproportionate for the degree of obesity and a positive family history of early-onset obesity may support a genetic analysis.

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**Corresponding author:**
Dr. Adela Chirita Emandi
Emergency Children’s Hospital “Louis Turcanu”
Iosif Nemoianu No 2; 300011, Timisoara, Romania
E-mail: adela.chirita@yahoo.com
CLINICAL AND EVOLUTIVE ASPECTS IN TAR SYNDROME - CASE REPORT

Marioara Boia, Valeria Belengeanu, Anca Popoiu, Dana Iacob, Aniko Manea, Lucica Stoica

University of Medicine and Pharmacy “Victor babes” Timisoara, Romania

Abstract
TAR syndrome is an rare autosomal recessive disorder characterized by severe thrombocytopenia and bilateral absent radii. A case of a newborn was presented, who has been hospitalized in the Premature and Neonatology Department, at 10 hours of age with a complex malformation. The clinical aspects and the results of the paraclinical investigation were suggestive for the diagnostic of TAR syndrome.

Key words: infertility, IVF procedures, balanced translocation, mozaicism

Introduction
TAR syndrome is an rare autosomal recessive disorder characterized by severe thrombocytopenia and bilateral absent radii. Extremely rare affection in current medical praxis, it was first described in 1951. TAR syndrome represents an association of malformations that includes many tissues and organs: gastro-intestinal (eg cow’s milk intolerance), skeletal (other abnormalities like hypoplastic or absence of ulna, abnormal or absent humerus and lower-extremity anomalies which occurs in 46% of patients etc), haematologic (severe thrombocytopenia at birth or during the first postnatal week occurs in 59% of patients with TAR, leukocytosis, anemia) and cardiac (atrial septal defect, tetralogy of Fallot in 1/3 of affected patients). Mortality is significant in the neonatal period and early infancy (first 14 months of life), primarily due to intracranial hemorrhage. Most of patients who died had platelet counts < 10.000/mmc. If the patient survives this period, spontaneous resolution of the thrombocytopenia usually occurs after the first year of age. Treatment is supportive with platelet transfusions given when needed.

Case report
A case of a newborn was presented, who has been hospitalized in the Premature and Neonatology Department, at 10 hours of age with a complex malformation: skull and facial dysmorphism, bilateral radial aplasia, intense systolic murmur and severe thrombocytopenia. The historical record of the newborn was not containing any special/ unusual elements: newborn female with the gestational age of 38 weeks, birth weight of 2750 g, natural born in cephalic presentation, APGAR score was 8/9, green amniotic fluid. There are no other malformations in her family.

The physical examination showed: influenced general state, pale tegument, perioronasal cyanosis, purple items over the chest, abdomen and lower- extremities (fig. 1a, 1b). Dismorphic facies, highly arched palate, low-implanted ears, micrognathia, short neck. Hypoplasia of the shoulder girth, short forearms, bilateral simian line (fig. 2). Cardiac system: precordial area was normal, cardiac frequency= 120/ min, gr. II/VI systolic murmur. Pulmonary system: normal conformed thorax, symmetrical respiratory movements, auscultation was normal, without pathological modifications. Examination of abdomen was also normal. Anterior fontanelle had ¾ cm, and it was normotensive. The archaic reflexes were reduced.

The paraclinical examinations confirm the clinical data, so:
The pelvis and upper extremities X-rays: short forearms with the congenital bilateral radial
aplasia, hands in extension with fingers in flexion-extension; normal pelvis (fig.3 and fig.4).

![Fig. 1a. Purple spots over the chest](image1)

![Fig. 1b. Purple spots over abdomen](image2)

The cardiac echography: normal cord with moderate septal hypertrophy. Atrial septal defect, respectively 0,3 cm foramen ovale with minimal left-right bridge.

The head ultrasonography:
- Bilateral periventricular leucomalacia – cystic form
- Second degree bilateral intraventricular haemorrhage.

The thoraco-abdominale X-rays, the ophthalmological, O.R.L. and neurological examinations did not give relevant evidence for the completion of the diagnosis.

The haemoculture was positive for Enterococcus faecalis. The peripheral cultures were negative.

The laboratory examinations made in dynamic specify the severe and persistent thrombocytopenia, associated with leukocytosis appeared in the infection, as shown in table 1.

The bone puncture and the medulograma were useful to confirm the diagnosis. In this case were detected: hypercellular smear through the predominant hyperplasia in all maturation compartments of the granulocyte series. Important eosinophilia which suggest an aspect of the leukemoid reaction. Is not distinguished pathological morphological modifications. The erythroblastic series- hypoplastic. The absence of the erythroblastic islands. Delayed hemoglobin synthesis. The megakaryocytic series- absent; few platelets on smear. The CIC System- moderately high infiltration with mature lymphocytes and lymphoides precursors. The reticuloendothelial system (RES)- high reactivity; macrophage was present; rare multinucleate cells.

**Conclusion:** Hypercellular bone marow through the hyperplasia of granulocyte series and reactive eosinophilia. Absent megakaryopoiesis. Stimulation of CIC system and RES.

![Fig. 2. Hypoplasia of the shoulder girth](image3)
The diagnosis was made following the presence of the thrombocytopenia and of the bilateral absence of the radius. The thrombocytopenia was present from the neonatal period with values between 13-14,000 and 30-45,000/mmc needed many platelet transfusions. The symptoms included disseminated purple items, petechiae, ecchymosis at the level of venous puncture and intracranial haemorrhage; they were certain data for the positive diagnosis. Unlike the cited cases in literature, in our case the thrombocytopenia did not worsened the intracranial haemorrhage, the intraventricular hyperechogenic formations were gradually absorbed.

The bilateral apasia of the radius was shown at the general physical examination and at the upper extremities x-rays. Also the patient presented the hypoplasia of the shoulder girth, the malposition of the fingers with the implantation in flexion of the thumbs. Patients with TAR syndrome always have thumbs and 4 digits associated with bilateral absence of the radii (fig. 5). According to some authors, the association of disparate skeletal and hematologic abnormalities is related to simultaneous development of the heart, radii, and megakaryocytes at 6 to 8 weeks gestation (5).

The exact pathophysiology of thrombocytopenia is still unclear.

The platelet abnormality reflects platelet hypoproduction, for which numerous explanatory theories have been proposed such as:

- a failure in production of humoral or cellular stimulators of megakaryocytogenesis (eg, thrombopoietin) is responsible for inhibiting platelet production; these studies (1, 2) showed comparable or increased levels of thrombopoietin in patients with TAR compared with healthy control subjects. These findings suggest that the thrombocytopenia is due to a lack of response.
to thrombopoietin, especially given the observation of normal thrombopoietin receptor expression on megakaryocytes. In 2000, Letestu et al suggested that the defect was a blockage in cell differentiation at an early stage(7);

• an abnormal response to stimulators of megakaryocytopoiesis involving an abnormal signal-transduction pathway(1);

• decreased numbers and sizes of megakaryocytic progenitor cells (2);
• abnormal progenitor cells with a maturational defect or receptor defect(7);
• the presence of humoral or cellular inhibitors of megakaryocytopoiesis (6).

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Table 1: Severe thrombocytopenia, in dynamic

Of the genetical point of wiew no causative mutation has been identified despite investigations of the c-mpl gene in patients with TAR. The link between osteodysgenesis and thrombocytopenia is unknow but suggests a common mechanism that affects embryonic development of the limbs and megakaryocytopoiesis. The HOX transcription factors have been considered candidate genes for TAR syndrome because their well-established function in limb development. The studies did not detect any abnormalities in individuals with TAR syndrome(3).

Evidence for autosomal recessive inheritance comes from families with several affected individuals born to unaffected parents, but several other observations argue for a more complex pattern of inheritance(4). Some studies described a common interstitial microdeletion of 200 kb on chromosome 1q21.1 at the studied patients with TAR. Analysis of the parents revealed that this deletion occurred de novo in 25% of affected individuals. Inheritance of the deletion along the maternal line as well as the paternal line was observed. The absence of this deletion in a cohort of control individuals argues for a specific role played by the microdeletion in the pathogenesis of TAR syndrome. The conclusion of this studies is that Deletion is associated with TAR syndrome but the phenotype develops only in the presence of an additional as-yet-unknown modifier(4).

Urban et al (1998) postulated that, given the phenotypic overlap between Roberts syndrome and TAR syndrome, allelic heterogeneity might cause both. In this postulate, TAR syndrome is the compound heterozygous form, with a mild and a severe mutation, whereas Roberts syndrome is the homozygous form with the severe mutation. However, genetic heterogeneity and environmental factors cannot be completely ruled out(8).

The associated malformations presented in literature were present in our case; so the patient had atrial septal defect, micrognathia, highly arched palate, low-implanted ears.
Althogh the cow’s milk intolerance appears in 47% cases in patient with TAR syndrome, our patient not presented this anomaly.

Besides thrombocytopenia, the laboratory examinations revealed leukytosis with values between 19,000- 35,000/mmcm which together with elevated sedimentation rate of red blood(30mm/h), positive hemoculture for Enterococcus faecalis and the influenced generale state needed antibiotherapy, having later a favorable evolution. Also the anemia was present and this required erythrocyte mass transfusions.

Conclusions
1. The clinical aspects were suggestive for the orientation of the diagnosis: dismorfic facies, highly arched palate, low-implanted ears, microgathnia, short neck, hypoplasia of the shoulder girth, short forearms;
2. The paraclinical investigations confirmed the diagnosis, the association between severe and persistent thrombocytopenia and the skeletal modifications being certain elements for positive diagnosis;
3. The caryotype modifications were not present and also no other cases with TAR syndrome in this family.

References
6. John K Wu et al, eMedicine, Thrombocytopenia- Absent Radius Syndrome.

Corresponding author:
Marioara Boia,
Gospodariilor Street, No. 42,
Timisoara 300778,
Romania
E-mail: marianaboia@yahoo.com
Romanian Society of Medical Genetics (SRGM)
Medical University “Victor Babes” – Timisoara
organizes

THE 9th BALKAN CONGRESS
OF MEDICAL GENETICS
15-17 September 2011, Timisoara, ROMANIA
Hotel Timisoara

www.balkancongress.srgm.ro
Dear Colleagues,

We believe that this scientific event will be a continuation of the previous eight successful meetings, held in various cities of the Balkan Peninsula.

In recent years, medical genetics has undergone profound changes and progress in the academic and medical level. European recommendations relating to treatment of rare genetic diseases network require collaboration between academic institutions and medical scientists from the region. In this spirit, we invite you to spend together a couple of days, combining science and research with a good mood!

BCMG Chairman of the Organizing Committee,
Prof. Dr. Maria Puiu

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(contains names of persons, in alphabetical order, which confirmed so far)

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PRELIMINARY SCIENTIFIC TOPICS

The Congress has a large thematic in genetics:

- Genomic Medicine; Genetic Diseases treatment;
- Clinical Genetics and dysmorphology;
- Population Genetics and genetic epidemiology;
- Reproductive Genetics; Pre and Perinatal Genetics;
- Cytogenetic; Molecular Genetics;
- Epigenetic factors and the development of human pathology;
- Cancer Genetics; Immunogenetics; Pharmacogenetics;
- Multifactorial Diseases; Psychiatric Genetics; Neurogenetics;
- Development defect and malformative syndromes; Fetopathology;
- Genetic Services; Genetic education; Ethics and bioethics;

Congress scientific informations:

Prof.univ.dr. Maria PUIU – Chairman
President of the Romanian Society of Medical Genetics
E-mail: maria.puiu@gmail.com

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**IMPORTANT DATES**

**September 15-17, 2011 – Congress dates**

**July 15, 2011** – Dead-line for early registration fee

**September 1st, 2011** – Dead-line for normal fee

**After September 1st, 2011** – On site fee

(Please register online via the conference homepage
www.balkancongress.srgm.ro)

**June 15, 2011** – Dead-line for abstract submission

(We cordially invite you to submit your abstracts in English language, online, at www.balkancongress.srgm.ro until June 15, 2011.)

**Medical exhibition**

The conference will host a medical exhibition. Interested companies are requested to contact “CONGRESS MASTER “ LTD for further information.

**VENUE – Timisoara Hotel**

(Marasesti street, no.1-4, Timisoara, Romania)

www.hoteltimisoara.ro

www. balkancongress.srgm.ro
GENERAL INFORMATION

TIMISOARA – The flowers’ city

Timișoara, the capital of the Banat Region of Romania, is situated in the west side of the country. It has around 350,000 inhabitants.

The city center largely consists of buildings from the Austro-Hungarian era. The old city consists of several historic areas. These are: Cetate (Belváros in Hungarian, Innere Stadt in German), Iosefin (Józsefváros, Josephstadt), Elisabetin (Erzsébetváros, Elisabethstadt), Fabric (Gyárváros, Fabrikstadt). Numerous bars, clubs and restaurants have opened in the old Baroque square (Unirii Square).

Landmarks include: Timisoara Orthodox Cathedral, St. George’s Cathedral (The Dome), Huniade Castle.

Performing arts: Romanian Opera House, Banatul Philharmonic of Timisoara, National, German and Hungarian State Theatre, Plai Festival – a world music and jazz festival.

Congress organizer company:

“CONGRESS MASTER” LTD – Timisoara
Laura Cuculescu – tel. +40-727-20.33.17
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Vice-President:

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➢ Lucian Negura
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➢ Aurelian Udristoiu, Vice-President of the Romanian Society of Laboratory Medicine
➢ Leon Zăgrean, Member, Academy of Medical Sciences of Romania

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Chairman:

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➢ Sloboda Dzhekova-Stojkova, Macedonia
➢ Najdana Gligorovic Barhanovic, Montenegro
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➢ Todor Gruiev, Macedonia
➢ Svetlana Ignjatovic, Serbia
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➢ Etleva Refatllari, Albania
➢ Martin Schwarz, U.K.
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➢ Tomris Ozben, Chair, IFCC Committee on Congresses and Conferences, Turkey
➢ Nazmi Ozer, Turkey
➢ Demetrios Rizos, Greece
➢ Milko Shishenkov, Bulgaria
➢ Orestes Tsolas, BCLF Board Honorary Individual Member, Greece
➢ Kamen Tzachev, Bulgaria
➢ Mira Winterhalter-Jadrić, Bosnia and Herzegovina
➢ Dogan Yucel, Turkey
The 19th BCLF Meeting is organized under the auspices of the:

- IFCC – International Federation of Clinical Chemistry and Laboratory Medicine
- WASPaLM – World Association of Societies of Pathology and Laboratory Medicine
- EFCC – European Federation of Clinical Chemistry and Laboratory Medicine
- Academy of Romanian Scientists
- Academy of Medical Sciences of Romania
- Romanian Academy, Section of Medical Sciences

Organized by:

- BCLF – Balkan Clinical Laboratory Federation

In collaboration with:

- Romanian Society of Laboratory Medicine
- Romanian Society of Medical Genetics
- Order of Biochemists, Biologists and Chemists in the Health System in Romania
- Romanian Neuro Psycho Endocrinology Society
- The OUTNOBEL FOUNDATION
- The Gheorghe BENGA FOUNDATION

Secretariat and management of services:

Wens Tour: Phone: +4 0264 590 749; Fax: +4 0264 595 755; E-mail: bclf@wens.ro
Website: www.wens.ro

Preliminary Scientific Topics:

- Education and training of specialists in laboratory medicine
- Accreditation of medical laboratories
- Quality control in laboratory medicine
- Molecular biology in diagnosis
- Genetic explorations (cytogenetics, biochemical genetics, molecular genetics)
- Inborn errors of metabolism
- Cardiovascular diseases, biochemical markers
- Lipids and lipid metabolism
- Metabolic syndrome
- Laboratory endocrinology
- Renal diseases, laboratory explorations
- Tumor markers and molecular diagnosis of cancer
- Hematology and coagulation
- Bone metabolism and diseases
- Infectious diseases
- Microbiology, antimicrobial susceptibility
- Proteins and proteomics
- Pharmacogenetics and personalized medicine
- Immunoassay and flow cytometry
- Point-of-care testing
- Trace and toxic elements
DATES TO REMEMBER

September 21-23, 2011: Meeting dates
May 1, 2011: Deadline for “Early bird” (reduced) registration fee
August 15, 2011: Deadline for Regular registration fee
August 21: Deadline for abstract submission

REGISTRATION FEES

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VENUE

The 19th BCLF meeting will be held in Rin Grand Hotel, in Bucharest, Romania

CITY

Romanian legend has it that the city of Bucharest was founded on the banks of the Dambovita River by a shepherd named Bucur, whose name literally means “joy.” His flute playing reportedly dazzled the people and his hearty wine from nearby vineyards endeared him to the local traders, who gave his name to the place. Known for its wide, tree-lined boulevards, glorious Belle Epoque buildings and a reputation for the high life (which in the 1900s earned its nickname of “Little Paris”), Bucharest Romania’s largest city and capital, is today a bustling metropolis, with many universities and research institutes, with old and new monuments and many outstanding museums waiting for your visit. A tour of Bucharest will be organized for participants in the BCLF Meeting.

WWW.BCLF-2011.ORG
ADDITIONAL INFORMATION FROM: gbgbenga@gmail.com
MANUSCRIPT REQUIREMENTS

General information
Manuscripts should be submitted to the Editor-in-Chief.
The Romanian Journal of Rare Disease (RJRD) is publishing high quality peer-reviewed articles from the entire spectrum of human rare disease.
Any manuscript submitted to the journal must not already have been published in another journal or be under consideration by any other journal.
Manuscripts submitted for publication must contain a statement mentioning that the institution’s ethics committee has approved all human and animal studies and all human studies have therefore been performed in accordance with the ethical standards laid down in an appropriate version of the 1964 Declaration of Helsinki. This statement must appear in the Methods section of the manuscript. For all articles that include information or photographs relating to individual patients, written and signed consent must be obtained from every patient prior to publish.
The manuscripts will be submitted electronically using the online submission system. Before submission, please make sure that the article is prepared according to manuscript requirements stated below. Two independent experts will review submitted articles.

Article types
Original articles: Should not exceed 4,000 words, including references and abstract.
Case reports: Up to 2,000 words, including references and abstract.
Review articles: Up to 6,000 words, including references and abstract.
Letter to the Editor: Up to 1,000 words.
Announcements of conferences, meetings, courses, awards, and other items likely to be of interest should be submitted with contact data. Up to 100 words.

Manuscript requirements
The manuscript must be in English, typed single space, one column on A4 paper, with margins: top - 3 cm, bottom - 2,26 cm, left -1,5 cm, right - 1,7cm. A 12-point font Times New Roman is required.
The manuscripts should be prepared according to the "Uniform requirements for manuscripts submitted to biomedical journals" (www.icmje.org). Each of the following components should begin on a separate page: Title Page, Abstract, Text, Acknowledgments, References, Tables and Figures.

1. Title page should include the following information:
   • Article title
   • Authors’ names and institutional affiliations connected through Arabic numbers.
   • The name of the department(s) and institution(s) to which the work should be attributed
   • Contact information for corresponding authors
   • Source(s) of support in the form of grants, equipment, drugs, or all of these

2. Abstract should state the purpose, basic procedures, main findings and principal conclusions of the study. The abstract must not exceed 2,000 characters (including spaces).

3. Text should be structured as followed:
   • Introduction
   • Material and methods
   • Results
   • Discussion and Conclusions

4. Acknowledgements of people, grants, funds, etc.

5. References. Citations in the text should be identified by numbers in square brackets. At the end of the paper they should be listed in numerical order corresponding to the order of citation in the text. The list of references should only include works that are cited in the text and that have been published or accepted for publication. The reference list should be structured in Vancouver style: names and initials of the first three authors, the title, source (journal abbreviations should conform to those in Index Medicus), year, volume and page numbers.
Example:

6. Tables and Figures should be followed by a legend numbered with Arabic numerals in order of appearance in the text and must include a brief, specific, descriptive title after the figure number.