MPS II phenotype: who recognizes this?

**Plaiasu Vasilica¹, Al-Khzouz Camelia²**

¹Regional Center of Medical Genetics Bucharest, INSMC Alessandrescu-Rusescu, Bucharest, Romania  
²Regional Center of Medical Genetics Cluj Napoca, Children’s Emergency Hospital Cluj Napoca, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

**Background**

*Mucopolysaccharidosis* (MPSs) are a group of lysosomal storage diseases, each of which is produced by an inherited deficiency of an enzyme involved in the degradation of acid mucopolysaccharidosis, called glycosaminoglycans (GAGs). The accumulation of GAGs increases the size of the lysosomes, which is why many tissues and organs are enlarged in this disorder. The Mucopolysaccharidosis share many clinical features but have varying degrees of severity.

*Mucopolysaccharidosis type II (MPS II), or Hunter syndrome* is a progressively debilitating disorder; however, the rate of progression varies among affected individuals. It leads to a wide variety of symptoms including distinctive coarse facial features, short stature, cardio-respiratory involvement, sensory organs pathology (changes in the eye, hearing impairments), and skeletal abnormalities. It manifests as a continuum varying from a severe to an attenuated form without neuronal involvement. Prevalence at birth in Europe is 1/166,000, and very rare cases of female presentation have been reported. The human *IDS* gene has been mapped to chromosome Xq28.1, spans approximately 24 kb, and contains 9 exons. The whole *IDS* gene has been sequenced, and an IDS-like pseudogene, comprising copies of exons 2 and 3 and intron 7, has been located about 20 kb from the active gene.
Materials and Methods

We present the results of enzymatic and genetic testing performed on 4 male patients experiencing abnormal phenotype referred to Genetics Department in the last four years.

Iduronate-2-sulfatase enzyme activity testing by fluorimetry method was performed on each patient in an international laboratory.

All patients with low enzyme activity were tested by molecular analyze on IDS gene using next-generation sequencing approach combined with classical Sanger sequencing + gel method and MLPA technique for deletion/duplication testing, PCR analysis with specific primers was performed followed by restriction digestion with Hinf1. The reference sequence was: NM_000202.5.

Case 1, 5 years 6 months

Familial history: mother=25 years, father=32 years, healthy; First child of the family
Personal medical details: birth at term, vaginal delivery
- morphometric measurements: Wt=24kg (90%), Ht=116cm (p75), OFC=52cm (p50)
- craniofacial dysmorphism (coarse facies, macrocrania, macrogloria, dental dystrophy, gum hypertrophy, short and broad neck)
- skeletal anomalies (limited movements of the joints for knees and elbows, hands joints; with limited movements, and joints stiffness, lumbar kyphosis)
- other: hepatosplenomegaly; umbilical hernia; hyperkinetic child, cognitive and speech delay, gait difficulties (on tips of the feet); cardiac murmur
Investigations: not performed
Clinical suspicion: MPS II

Case 2, 2 years 7 months

Familial history: mother=30 years, father=29 years, a brother=8 months, all are healthy, First born child of the family
Personal medical details: birth at 38 weeks of gestational age, cesarean section, maternal-fetal infection, weight=3100g, length=52cm, APGAR score 9, prolonged jaundice, mild developmental delay (he walked alone around age of 2 years), recurrent respiratory infections, adenoïdectomy
Clinical picture at age of 5 years 6 months (before diagnosis):
- morphometric indicators: Wt=14kg (p95), Ht=100cm (p95), OFC=54cm (p95)
- craniofacial dysmorphism (coarse facies, macrocrania, macrogloria, thick lips, frontal bossing, gum hypertrophy, broad nasal bridge)
- dry skin, dermatitis, hirsutism
- skeletal anomalies (limited movements of the joints for knees , elbows, pectoral, lumbar kyphosis)
- other: hepatosplenomegaly; umbilical hernia; hyperkinetic child, cognitive and speech delay, attention deficit
Investigations: not performed
Clinical suspicion: MPS II

Case 3, 1 year 4 months

Familial history: mother=28 years, father=33 years, with psoriasis ; First child of the family
Personal medical details: birth at 39 weeks of gestational age, cesarean section, weight=4400g, length=57cm, APGAR score 9, prolonged jaundice, he sat down at age of 6 months 2 weeks, he walked alone around age of 1 year
Clinical picture at age of 1 year 4 months:
- morphometric values: Wt=14kg (p95), Ht=90cm (p95), OFC=50cm (p95); macrosomia
- craniofacial dysmorphism (coarse facies, gum hypertrophy, broad nasal bridge, closed anterior fontanel)
- skeletal anomalies (limited movements of the joints for knees, elbows, scapulo-humeral joints, pectoral carinatum, lumbar kyphosis
- hepatomegaly; hyperkinetic child, he smiles, he answers to our requests
Investigations: abdominal echography: normal; mild anemia at age of 9 months; liver function, lipid profile: normal results
Clinical suspicion: MPS II

Case 4, 4 years 8 months

Familial history: mother=31 years, father=34 years, a healthy sister
Personal medical details: birth at term 38 weeks of gestational age, cesarean section, weight=3050g, length=50cm, OFC=33,5cm, APGAR=9; he started walking at age of 1 years 4 months
Inguinal hernia in infant period (3 months), adenoïdectomy at age of 3 years 6 months, seizures with fever at age of 2 years 4 months, snoring during the night
Clinical picture at age of 4 year 8 months:
- morphometric parameters: weight=17kg(p50), height=106cm(p25-50), OFC=53,5cm(+2DS)
- craniofacial dysmorphism (coarse facies, gum hypertrophy, broad nasal bridge, mild macrosomia)
- skeletal anomalies: limited movements of the joints for knees, elbows, scapulo-humeral joints, broad joints of the knees, mild kyphosis
- cardiac murmur
- he smiles and talks, he answers to our requests, with limiting of fine motor skills
Investigations: normal abdominal echography, ocular evaluation with myopic astigmatism, mild hepatic cytolyosis, normal creatin kinase, glycaemia, blood counting
Clinical suspicion: MPS II
Results

- **MPS II**

- **Gender**: Female
- **Age of diagnosis**: 20 months
- **Genetic and clinical diversity of mutations associated with MPS II**

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**Discussion**

- Early recognition of MPS II requires careful attention to the presence of multiple signs and symptoms, many of which overlap with common childhood complaints.
- Coarse facial features are a strong diagnostic clue of an LSD and are manifest in MPS II patients.
- Early skeletal signs include joint stiffness and restricted range of motion.
- A history of frequent and recurrent surgeries in young children is a defining characteristic of MPS II.
- Developmental delay and/or speech delay is recognized in severe phenotype only.
- Enzyme assays are considered the gold standard for diagnosis of MPS II.
- Genetic testing of the IDS locus is the only reliable way to identify female carriers of the disease.
- To date, more than 541 different mutations underlying MPS II have been identified.
- The frequency of large alterations (complete or partial gene deletions and large rearrangements) is about 28.2%, however, the majority of the identified mutations (71.8%) are small deletions, insertions, or single base substitutions (missense mutations, nonsense mutations, and mutations affecting splicing).
- In terms of genotype-phenotype correlations deletions or rearrangements of the IDS gene that completely abolish idS transcript production will result in the severe phenotype. The intron 7 of the IDSs is a recombinant hotspot. The missense variant p.Ser333Leu is one of the most common variants. It has been associated with a neuropathic phenotype.

**Pitfalls in diagnosis of MPSII:**

1. failure to link the many, seemingly unrelated signs and symptoms experienced by the patient into a single syndrome
2. existing a positive family history
3. the MPS II phenotype can vary even among family members who share the same IDS mutation
4. diagnosis of MPS II cannot be ruled out based on female gender
5. every specialist could have a patient with MPS phenotype
Conclusions

➢ The clinical description remains an important first step in focusing biochemical and genetic testing.

➢ Frequently there is a significant delay between the appearance of symptoms and the final diagnosis for MPS patients.

➢ A medical geneticist can help to choose the suspected clinical entity and genetic test, based on current test methodology for a more accurate diagnosis.

➢ There is a lack of genotype-phenotype correlations in MPS II.

➢ The identification of carriers through mutational studies is important for genetic counselling and prenatal diagnosis.

➢ Nurses need to be able to recognize warning signs of the disease and be educated enough to provide competent care.

➢ All professionals could have an active role in identifying of patients with suspected abnormal phenotype of MPS. Multidisciplinary approaches are needed.

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References


