Disorders: Metachromatic leukodystrophy, Morquio A syndrome, Sanfilippo A syndrome, Sanfilippo D syndrome, Maroteaux Lamy syndrome, which are autosomal recessive conditions, Hunter syndrome, which belongs to the group of X-linked disorders, as well as X-linked types of ichthyosis and chondrodysplasia punctata.

Patients with MSD carry the phenotypical features of these disorders. Psychomotor retardation, coarse face, ichthyosis, and skeletal findings like scoliosis and dysostosis multiplex are the most common findings of the disease. Based on the degree of severity and age of onset, neonatal, moderate, and mild types of MSD have been differentiated.

Here, we present clinical findings and the mutation analysis of four Turkish patients with MSD.

Case Reports

The patient 1 was a 1.5-year-old girl who was admitted to our hospital for developmental delay and epilepsy. Her parents were not consanguineous. She was hypotonic, mentally retarded and unable to sit and walk. Upper and lower tendon reflexes were absent and Babinski sign was bilaterally negative. She also had coarse face, ichthyosis, hypertrichosis,
In the four patients, clinical findings suggested MSD and the enzymatic assays of three different sulfatases (Arylsulfatase A, Arylsulfatase B, and Iduronate Sulfatase) revealed very low levels of the enzymes [Table 2]. These were also confirmed by DNA analysis and the four patients were homozygous for a missense mutation c. 739G > C causing a p.G247R amino acid substitution in the SUMF1 gene.

Discussion

MSD is a rare autosomal recessive inborn error of metabolism. Its prevalence is 1 in 1 million births. Worldwide, less than 50 cases have been published so far.[1]

MSD is primarily a defect in the posttranslational modification of sulfatase to its active form. FGly is the key catalytic residue within the active catalytic side of sulfatases, and it is converted from cysteine by the action of formylglycine-generating enzyme (FGE).[6] This enzyme is defective in MSD. The gene encoding for FGE, known as SUMF1, has been identified and disease-causing mutations have been described.[7]

The clinical picture of MSD combines symptoms of the different sulfatase deficiencies. Patients show neurological deterioration and a neurodegenerative course of disease similar to metachromatic leukodystrophy. In addition, developmental delay, dysmorphism, and organomegaly are present as found in various mucopolysaccharidoses. Skeletal abnormalities remind one of Chondrodysplasia punctata type I and skin changes of X-linked ichthyosis.[1,4] Patients with MSD may also have mental retardation, coarse face, seizures, leukodystrophy, tetraplegia, visceromegaly, ichthyosis, and dysostosis. Early development may be normal following an often rapid clinical progression, with neurodegeneration leading to early death within a few years of clinical onset.[1]

Clinical manifestations are markedly variable in patients with MSD. The neurological progression may be slow and there may be no hepatosplenomegaly that is typical for MSD. Patients may have corneal clouding, macrocephaly, dysostosis multiplex, and mild mental retardation, but...
Table 1: Demographic findings of all patients

| Clinical and MRI findings | Patient 1 | Patient 2 | Patient 3 | Patient 4 |
|--------------------------|-----------|-----------|-----------|-----------|
| Age/sex (month)          | 18/F      | 11/M      | 18/F      | 16/F      |
| Epilepsy                 | ±         | ±         | ±         | ±         |
| Congenital cardiac defect| ±         | ±         | ±         | ±         |
| Hypotonia                | ±         | ±         | ±         | ±         |
| Deafness                 | -         | -         | ±         | ±         |
| Ichthyosis               | ±         | ±         | ±         | ±         |
| Dysostosis multiplex     | ±         | ±         | ±         | ±         |
| MRI findings             | ±         | ±         | ±         | ±         |
| Hepatosplenomegaly       | ±         | ±         | ±         | ±         |
| Dismorphic findings      | ±         | ±         | ±         | ±         |
| Developmental delay      | ±         | ±         | ±         | ±         |
| Growth retardation       | ±         | ±         | ±         | ±         |

MRI=Magnetic Resonance Imaging

Table 2: Enzymatic assays of three different sulfatases measured in patients

| Patient | ARS A (50-250 nmol/mg/h) | ARS B (10-50 nmol/mg/h) | IDS (494-1113 nmol/mg/4 h) |
|---------|---------------------------|--------------------------|-----------------------------|
| 1       | 0.93                      | 0.51                     | 15                          |
| 2       | 3.58                      | 0.1                      | 18.3                        |
| 3       | 5.5                       | 0.2                      | 12                          |
| 4       | 8.4                       | 0.2                      | 10.5                        |

ARS A=Arylsulphatase A, ARS B=Arylsulphatase B, IDS=Iduronate sulphatase

Conclusion

It is important to consider the possibility of MSD in a child with skin problems and neurological deterioration. Detailed skin and physical examination is mandatory in a neurology clinic in a patient with either metachromatic leukodystrophy or mucopolysaccharide deficiency. Molecular genetic analysis of the SUMF1 gene should be performed to elucidate the disease causing mutation as a prerequisite for precise genetic counseling and prenatal molecular genetic diagnosis.

References

1. Hopwood JJ, Ballabiao A. Multiple sulfatase deficiency and the nature of the sulfatase family. In: Scriver CR, Baudet AL, Sly WS, editors. The Metabolic and Molecular Basis of Inherited Disease. 8th ed. Vol. III. New York: McGraw-Hill; 2001. p. 3725-32.
2. Dierks T, Schlotawa L, Frese MA, Radhakrishnan K, von Figura K, Schmidt B. Molecular basis of multiple sulfatase deficiency, mucolipidosis II/III and Niemann-Pick C1 disease - Lysosomal storage disorders caused by defects of non-lysosomal proteins. Biochim Biophys Acta 2009;1793:710-25.
3. Schmidt B, Selmer T, Ingendoh A, von Figura K. A novel amino acid modification in sulfatases that is defective in multiple sulfatase deficiency. Cell 1995;82:271-8.
4. Ballabiao A, Shapiro LJ. Steroid sulfatase deficiency and X-linked ichthyosis. In: Scriver CR, Baudet AL, Sly WS, editors. The Metabolic and Molecular Basis of Inherited Disease. 8th ed. Vol. III. New York: McGraw-Hill; 2001. p. 4241-62.
5. Schlotawa L, Steinfeld R, von Figura K, Dierks T, Gärnter J. Molecular analysis of SUMF1 mutations: Stability and residual activity of mutant formylglycine-generating enzyme determine disease severity in multiple sulfatase deficiency. Hum Mutat 2008;29:205.
6. Dierks T, Dickmanns A, Preusser-Kunze A, Schmidt B, Mariappan M, von Figura K, et al. Molecular basis for multiple sulfatase deficiency and mechanism for formylglycine generation of the human formylglycine-generating enzyme. Cell 2005;121:541-52.
7. Annunziata I, Bouchè V, Lombardi A, Settembre C, Ballabio A. Multiple sulfatase deficiency is due to hypomorphic mutations of the SUMF1 gene. Hum Mutat 2007;28:928.
8. al Ageel A, Ozand PT, Brismar J, Gascon GG, Brismar G, Nester M, et al. Saudi variant of multiple sulfatase deficiency. J Child Neurol 1992;7:S12-21.
9. Yiş U, Pepe S, Kurul SH, Ballabio A, Cosma MP, Dirik E. Multiple sulfatase deficiency in a Turkish family resulting from a novel mutation. Brain Dev 2008;30:374-7.
10. Cosma MP, Pepe S, Parenti G, Settembre C, Annunziata I, Wade-Martins R, et al. Molecular and functional analysis of SUMF1 mutations in multiple sulfatase deficiency. Hum Mutat 2004;23:576-81.

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