ORIGINAL ARTICLE

EPIDEMIOLOGY AND RELATIVE INCIDENCE OF RARE NEUROMETABOLIC AND NEUROGENETIC DISORDERS IN IRAN

Yousef Shafeghati MD*, **•, Roxana Karimi-Nejad MS**, Farnaz Azimi BS**,
Mohammad-Hassan Karimi-Nejad MD**, Jan G. M. Huijmans MD, PhD***,
Wim J. Kleijer MD, PhD***, Otto P. Van Digglen MD, PhD***

*University of Welfare and Rehabilitation, Nationwide Genetic Counseling
Network, Tehran, ** Dr. Karimi-Nejad Genetic Center, Tehran, Iran,
***Genetic and Metabolic Department of Erasmus University, Rotterdam, Netherlands*

Abstract

Background-With prevalent consanguineous marriages taking place in Iran, the probability of the incidence of some rare metabolic disorders are anticipated to be higher in this population.

Methods-In a 10-year period, 128 families including 196 cases referred to the Dr. Karimi-Nejad Genetic Center with neurometabolic and neurogenetic disorders were evaluated. The diagnosis of suspected cases of "inborn errors of metabolism" were confirmed in collaboration with the Genetics and Metabolic Department of Erasmus University, Rotterdam.

Results-Among the surveyed families, mucopoly-saccharidoses (MPS) was present in 41 families with 52 affected members, lipid storage diseases in 48 families with 77 patients and micromolecular metabolic disorders in 39 families with 67 affected members. In 50 families, prenatal testing showed 11 (22%) affected fetuses. In some instances, very rare metabolic disorders were observed, which were not previously reported in Iran.

Conclusion-This study shows that in a population with high incidence of consanguineous marriages, some rare metabolic disorders are relatively common. Preventive measures including genetic counseling and detection of high-risk families by detailed investigation of index cases and appropriate family members are mandatory. Based on this information, detection of affected fetuses by prenatal testing is recommended.

Keywords • Neurometabolic • neurogenetic • inborn errors of metabolism
• genetic counseling

Introduction

Metabolic disorders caused by genetic mutations and enzyme deficiencies constitute a wide spectrum of diseases in mankind. Since Archibald Garrod first introduced the term "inborn errors of metabolism" at the beginning of the 20th century, more than 300 hereditary metabolic disorders have been discover-ed. Over one-third of such disorders are characterized by CNS involvement and regressive neurologic symptoms, most of which are transmitted by the autosomal recessive inheritance pattern. Enzyme deficiencies cause defects in the synthesis, metabolism, transportation and storage of biochemical compounds, which in turn may lead to tissue intoxication or energy deficiency in vital organs like the brain, eyes, heart, muscles, liver and kidneys.

These inborn errors are classified by their anatomic location (cerebral gray or white matter),

•**Correspondence:** *Y. Shafeghati MD, University of Welfare and Rehabilitation, Tehran, Iran. Fax: +98-21-2407814.*

size of the molecule or metabolite involved (small or large), age of onset (early or late), mechanism of action (intoxication or energy deficiency) and neurologic manifestations (acute or chronic, static or progressive). Generally, these metabolic disorders can be classified into two main groups: macromolecular and micromolecular.

Micromolecular metabolic diseases are generally characterized by their acute and very early (neonatal/early infantile) onset, their rapid progression, poor prognosis and fetal outcome.

Macromolecular diseases tend to occur in later infancy, childhood and even in adulthood. Most macromolecular metabolic disorders are lysosomal storage disorders (glycogens, lipids, mucolipids, and mucopolysaccharides). Late onset, slow progression, neurologic regression, ataxia, spasticity, poor vision, hearing loss, and progression to dementia are some of their most common signs and symptoms.

In most of these metabolic disorders, the CNS white matter is affected first, but eventually both gray and white matter is involved.

As consanguine marriages are very common in Iran, it appears that the incidence of rare metabolic disorders would be very high in this population. In this article, patients with different metabolic disorders referred to our genetic center in a ten-year period are briefly reviewed.

Patients and Methods

Over a 10-year period, 128 families including 196 patients, have been referred to the Dr. Karimi-Nejad Genetic Center with at least one of the manifestations mentioned in Table 1.

Table 1. The main causes of referral of patients and their families.

History of death in one or more children
History of mental retardation
Seizure or ataxia
Deafness or blindness
Coarse facies and hirsutism
Behavioral disorders
Muscular wasting
Neurologic regression
Skeletal and joint deformity

Table 2. Relative incidence of patients with sphingolipidosis and results of prenatal diagnosis in affected Iranian families.

Type of disease	Number of families	Affected members	Prenatal diagnosis	Affected fetuses	Normal
MLD	10	12	2	1	1
Niemann-Pick	7	12	6	1	5
Gauchers	5	8	1	-	1
Tay-Sacks	4	4	1	1	-
Mucolipidosis	4	5	3	-	3
Canavan	3	8	-	-	-
Alexander	3	3	-	-	-
Sandhoff	2	4	2	1	1
GM1-Gangliosis	1	5	1	-	1
Fabry	2	5	-	-	-
Fucosidosis	1	1	1	-	1
NCLF**	2	3	-	-	-
SBH***	1	2	-	-	-
Lipidosis	3	5	-	-	-
Total	48	77	17	4	13

*MLD: Metachromatic leukodystrophy, ** NCLF: Neuronal ceroid lipofuscinosis, ***SBH: Sea blue histiocytosis

A detailed medical record was created for consulting index cases and prenatal, postnatal, personal and family histories were put together. A complete family pedigree was constructed later. Depending on availability, copies of the patients' hospital, pathology and autopsy reports were obtained. Further consultations or investigations were carried out according to request; EMG, NCV, EEG, brain CT or MRI scanning, provocative visual and auditory tests, bone marrow aspiration for abnormal histiocytes, skeletal survey for dysostosis multiplex and in some instances, peripheral nerve or brain biopsy.

According to all available data, we proposed probable and differential diagnoses. For the confirmation of diagnoses as well as the conduction of necessary enzyme assays, the appropriate urine and blood specimens and skin biopsy samples in culture media were sent to the Genetic and Metabolic Department of Erasmus University, Rotterdam.

Table 3. Relative incidence of MPS and its prenatal diagnosis in affected Iranian families.

Type of disease	Number of families	Affected members	Prenatal diagnosis	Affected fetuses	Normal
MPS III	15	19	9	1	8
MPS IIIA	*7*	*9*	*4*	*1*	*3*
MPS IIIB	*6*	*7*	*5*	*-*	*5*
MPS IIID	*1*	*1*	*-*	*-*	*-*
MPS III?	*1*	*2*	*-*	*-*	*-*
MPS II	10	17	5	1	4
MPS I	8	8	4	2	2
MPS VI	6	5	6	-	6
MPS IV	1	1	-	-	-
MPS ?	2	3	-	-	-
Total	42	53	24	4	20

Results

According to the collected data, after complete investigation and enzyme assays, 48 families with 77 patients were included in the category of lipid storage diseases (Table 2). The most common type of these disorders were metachromatic leukodystrophy (Figure 1), followed by Niemann-Pick, Gauchers, and Tay-Sachs diseases. We were also confronted with families suffering from mucolipidosis, Canavan, Alexander and Sandhoff diseases. In this study, a family with 5 affected siblings with the final diagnosis of GM1 gangliosidosis was identified; the parents were first cousins.

In 41 families with 52 index cases, the final diagnosis was mucopolysaccharidoses (Table 3). Type III was most common with 15 affected families. Type IIIA, IIIB and IIID were detected in 7, 6, and one families, respectively. Type II-MPS (Hunter syndrome) was the next most common type, followed by type I (Hurler syndrome). Interestingly, type III was more common among these patients, while in the medical literature, type I-MPS is stated to be the most prevalent (Figure 2).

Micromolecular metabolic diseases were the third category in these patients and the relative incidence of their different types is shown in Table 4. Organic acidemias were the most common disorders. A total of 39 families had 67 affected

individuals, many of whom had been diagnosed primarily by enzyme analysis.

Prenatal testing by chorionic villus sampling or amniocentesis, which was carried out for 50 families, showed that 11 (22%) fetuses were affected.

Discussion

A useful diagnostic approach is to consider the frequency of neurometabolic disorders in the pediatric age group. The type of diseases recognized in different specialty centers depend on referral patterns and on ethnic, geographic, and genetic factors. Nevertheless, it is informative to have some knowledge about the relative frequency of inborn errors of metabolism in a given

Table 4. Relative incidence of micromolecular metabolic disease and its prenatal diagnosis in affected Iranian families.

Type of disease	Number of families	Affected members	Prenatal diagnosis	Affected fetuses	Normal
Organic acidemia	11	20	-	-	-
Metylmalonic A.	3	5	-	-	-
Isovaleric A.	1	2	-	-	-
Propionic A.	1	1	1	-	1
Unknown	6	12	-	-	-
Galactosemia	2	3	1	-	1
Lesch-Nyhan	2	4	1	1	-
Tyrosinemia	2	4	1	-	1
GSD I,III	2	2	-	-	-
MSUD	1	1	-	-	-
AT	1	2	1	1	-
XP	3	5	3	1	2
Cockyne	1	1	-	-	-
CF	2	4	1	-	1
GTD (RP)	1	1	-	-	-
Total	39	67	9	3	6

GSD: glycogen storage disease, MSUD: maple syrup unrine disease, AT: ataxia telangectasia, XP: xeroderma pigmentosum, CF: cystic fibrosis, GTD (RP): geographic tapetoretinal degeneration (retinitis pigmentosa).

Figure 1. A 5-year old girl who was suffering from metachromatic leukodystrophy.

population. Saudubray, et al who studied 326 infants in Paris and McKusick who studied 119 patients gathered some valuable information in this field. In Saudubray's study, aminoacidopathies, organic acidurias and hyperammonemias were the most common inborn errors of metabolism (31.3%, 27%, and 20.8% of all cases, respectively), while in McKusick's study, organic acidurias were

Figure 2. Hurler's disease (MPS I). Note the coarse facies, short stature, joint deformity, umbilical hernia, cloudy cornea and mental retardation.

found to be the most common form [42%], followed by aminoacidopathies and lysosomal storage diseases [16.8% each].

In our series, the frequency of micromolecular disorders is less common than the study of Saudubray, Borden, and McKusick since most of these patients remain undiagnosed in early infancy. Macromolecular disorders are, however, more common because they are mostly of late onset and progress slowly.

A great number of our patients had been referred with neurologic regression and loss of previously acquired and developed milestones.

Consanguineous marriages are very common in our society. In some areas, its prevalence exceeds 50% of all marriages because of social, cultural, and religious background. Eighty-two percent of the parents who participated in this study were close relatives, mostly first cousins.

Pre-marriage or pre-conceptional genetic counseling would be helpful and could sometimes help in the detection of high-risk families or pregnancies. In these circumstances, by having precise diagnosis at hand and by rational use of prenatal diagnostic methods, detection of affected fetuses is not difficult.

References

1 Garrod A. Inborn Errors of Metabolism. *Lancet*; 1908.
2 Iafolla AK, McConkie-Rosell A. Prenatal diagnosis of metabolic disease. *Clin Perinato.* 1990; **17:** 761-77.
3 McKusick V. *Mendelian Inheritance in Man.* 9th ed. Baltimore: Johns Hopkins University Press; 1991.

4 Scriver CR. *The Metabolic Basis of Inherited Disease*. 6th ed. New York: McGraw-Hill; 1989.

5 Saudubray JM. *Inborn Errors of Metabolism*. Vol 24. New York: Raven. Nestle Nutrition Workshop Series. 1991; 137.

6 Swick HM. Diseases of gray matter. In: Swaiman KF, ed. *Pediatric Neurology. Principles and Practice*. St Louis: Mosby; 1989: 777.

7 Matlon RK. Lipid storage disorders. In: Nelson WE, ed. *Nelson's Textbook of Pediatrics*. 15th ed. Philadelphia:

WB Saunders; 1996.

8 Fenichel GM. *Clinical Pediatric Neurology. A Sign and Symptom Approach*. 2nd ed. Philadelphia: WB Saunders; 1993.

9 Borden M. Screening for metabolic diseases. In: Nyhan WI, ed. *Abnormalities in Amino Acid Metabolism in Clinical Medicine*. Norwalk: Appleton Century Crofts; 1984: 401.

10 Jones JD. Screening tests for inherited metabolic diseases. *Mayo Clin Proc*. 1984; **59:** 347-9.