Middle East Journal of Family Medicine, 2004; **Vol**. **6** (6)

COMMON GENETICS AND METABOLIC DISEASES IN SAUDI ARABIA

Aida I Al-Aqeel MD DCH FRCP (Lond), FRCP (Edin), FACMG

Department of Paediatrics, Riyadh Armed Forces Hospital and Department of Genetics, King Faisal Specialist Hospital

Correspondence:
Dr Aida Al Aqeel MD, DCH, FRCPLond FRCPEdin FACMG
Consultant Paediatric Metabolist,
Geneticist and Endocrinologist
Department of Paediatrics
Riyadh Armed Forces Hospital
P O Box 7897
Riyadh 11159
Saudi Arabia
Tel: +966-1-4777714 Ext 5452
Fax: +966-1-4777714 Ext 4603
Email: aidaibrahim@hotmail.com

Keywords: Genetics metabolic disorders; Inborn errors of metabolism; Saudi Arabia

Abstract
Middle Eastern cultures are tribal and heavily consanguineous. Marriage between cousins has been part of the culture for millennia leading to "founder" effect and a large number of autosomal recessive diseases.

In Saudi Arabia like other Middle East countries first cousin marriages account for 60 - 70% of all marriages, leading to uniquely common disorders which are either rare by Western standards or are unknown. The practicing physician must include these unusual disorders in his diagnostic considerations, since cybernetic trees described for European countries or USA may not be valid for the Middle East.

A review of the combined files of the Armed Forces Hospital and the King Faisal Specialist Hospital and Research Centre, Riyadh, over 10 years period, documented more

than 150 varieties of neurodegenerative disease among 2,000 children; 27 of which constitute more than half of these files (Table 1). Some autosomal recessive disorders are common e.g. sickle cell anaemia and thalassaemia. Others are unique e.g. Sanjad Sakati syndrome and Al-Aqeel-Sewairi syndrome. In these disorders the exact molecular defect is found. Therefore, prevention is possible by either pre-implantation genetics diagnosis or prenatal diagnosis according to the recommendation of our Islamic leaders.

These diseases are clinically recognizable through certain symptoms and signs which are summarized in table II.

Their early recognition is important to initiate treatment and to prevent neurologic crippling. The treatment of storage diseases is experimental and is either through administration of purified enzymes (Ceredase-Gaucher) or bone marrow transplantation (Gaucher type II, Niemann Pick-B, Morquio's disease A). The therapeutic modalities of the other treatable diseases are shown in Table III.

A review of these tables indicates that a large number of these genetic metabolic disorders can be recognized in a clinical setting and have treatment modalities. However, treatment is either difficult or expensive or unavailable in most centers. Therefore, prevention is of utmost importance.

References

1. Saudubray JM, Charpentier C. Clinical phenotypes: diagnosis/algorithms. In: Seriver CR, Beaudet AL, Sly WS, Valle D. editors. The metabolic and molecular bases of inherited disease. 7th ed. McGraw Hill, 1995; 327-400.

2. Ozand PT, Gascon GG. Organic acidurais: a review, part 1 and part 2. J Child Neurol 1991; 6:1956-219 and 288-303.

3. Ozand PT, Gascon GG, Al Aqeel A., Roberts G, Dhallaa S, Sarvapelli SB. Prevalence of different types of lysosomal storage diseases in Saudi Arabia. J Inherit Metab Dis 1990; 13: 849-861.

4. Al Aqeel A, Ozand PT, Brismar J, Gascon GG, Brismar G, Nester M, Sakati N. Saudi variant of multiple sulfatase deficiency. J Child Neur, 1992; 7: S12-S21.

5. Al Aqeel A, Ozand PT, Gascon G, Nester M, Al Nasser M, Brismar J, Blau N, Hughes H, Subramanyaaan SB and Reynolds CT. Biopterin-dependent hyperphenylalaninemia due to deficiency of 6-pyruvoyl tetrahydropterin synthase. Neur 1991; 41: 730-737.

6. Sanjad SA, Sakati NA, Abu-Osba YK, Kaddora R, Milner RDG. A new syndrome of congenital hypoparathyroidism, seizure, growth failure and dysmorphic features. Archives of Diseases Childhood 66: 193-196, 1991.

7. Parvari R, Hershkovitz E, Grossman N, Gorodischer R, Loeys B, Zecic A, Mortier G, Gregory S, Sharony R, Kambouris M, Sakati N, Mayer BF, Al Aqeel A et al. Mutation of TBCE causes hypoparathyroidism-retardation-dysmorphism and autosomal recessive Kenny-Caffey syndrome. Nat Genet 2002 Nov; 32(3): 448-52.

8. Al Aqeel AI, Al Sewairi W. Al Aqeel Sewairi Syndrome: an autosomal recessive syndrome with nodular arthropathy and acrolysis. American Journal of Human Genetics, October 1999; 65(4), 750.

9. Al-Aqeel AI, Al Sewairi W, Edress B, Gorlin RJ, Desnick R and Martignetti J. Inherited multicentric osteolysis with arthritis: a variant resembling Torg syndrome in a Saudi family. American J Medical Genetics 2000; 93:11-18.

10. Martignetti JA, Al Aqeel A, Al Sewairi W, Boumah C, Kambouris M, Al Mayouf S, Sheth KV, Al Eid W, Dowling O, Harris J, Glucksman MJ, Bahaabri S, Meyer BF and Desnick RJ. Mutation of the matrix metalloproteinase 2 gene (MMP2) causes multicentric osteolysis and arthritis syndrome. Nature Genetics 2001; 28: 261-265.

11. Al Aqeel AI, Serdar C, Sakati N, Jarodi K, Ozand P, Hellani A. Pre-implantation genetic diagnosis for Sanjad-Sakati syndrome. American Journal of Human Genetics Nov 2003; 73(5): 2502.

12. Ozand PT. Gascon GG. Treatment of inherited neurometabolic diseases: the future. J Child Neurol 1992; 7:S132-S140.

13. Acosta PB. Ross metabolic formular system nutrition support protocols. Columbus, Ohio: Abbott Laboratories, 1997.

TABLE 1 - COMMON GENETIC AND METABOLIC DISEASES

The common diseases are listed, in descending order of frequency, and total approximately 80 per cent of each category

Disease	Number (%)	Disease	Number(%)	Disease	Number (%)
Lymsosomal3 storage diseases(N=324)		Carbohydrate & lipid disorders (N=156)		Organic acidaemias2(N=455)	
Niemann Pick disease	51 (16%)	Glycogen storage disease T.3	31 (20%)	Methylmalonic acidaemia	76 (17%)
Morquio's disease	35 (11%)	Fructose diphosphatase deficiency	27 (18%)	Propionic acidaemia	63 (14%)
Sandhoff's disease	31 (10%)	Glycogen storage disease T.1	22 (14%)	Biotinidase deficiency	41 (9%)
Multiple sulphase deficiency (Saudi variant)	27 (8%)	Galactosemia	20 (13%)	Canavan's disease	41 (9%)
Galactosialidosis	25 (8%)	Hypercholesterolaemia Type I	20 (13%)	Fatty acid oxidation defects	36 (8%)
Hurler-Scheie disease	24 (8%)	**Aminoacidaemias (N=253)**		3-Methylglutaconic aciduria	32 (7%)
Gaucher's disease	20 (6%)	Maple syrup urine disease	75 (30%)	HMG CoA lyase deficiency	25 (5%)
Neuronal ceroid lipofuscinosis	16 (5%)	Classic PKU	47 (19%)	Pyruvate carboxylase deficiency	20 (4%)
Hunter syndrome	16 (5%)	Homocystinuria	43 (17%)	Glutaric aciduria type I	20 (4%)
Sanfilippo syndromes	15 (5%)	6-PTS deficient PKU5	24 (10%)	Isovaleric acidaemia	15 (3%)
		Non-ketotic hyperglycinaemia	12 (5%)	Unique genetic syndromes (N=60)	
				Sanjad-Sakati syndrome	40 (60%)
				Al-Aqeel Sewairi syndrome	20 (30%)

TABLE II - ALERTING SIGNS FOR COMMON GENETIC METABOLIC DISEASES	
Disease	**Alerting sign**
Glycogen storage type 1	Type 1a: Severe, and early hepatomegaly reaching iliac crest, early morning hypoglycemia and lactic acidosis. Type 1b: same features; frequent infections due to neutropenia
Galactosemia	Early hepatomegaly, jaundice, failure to thrive, cataract
Hypercholesterolaemia type I	Eruptive xanthomas, family history of untimely death due to cardiac or CNS infarcts
Maple syrup urine disease	Classical form: Onset 1-2 weeks after birth with lethargy, coma, alternating tone changes, seizures with no associataed hypoglycemia, acidosis nor hyperammonemia
Classic PKU	Fair features in an Arab child, with 3-9 months onset of myoclonic seizures, mental handicap and aggressive behaviour later in childhood in untreated patients.
Homocystinuria	Shy infant with early dislocation of the lens downwards, the arachnodactyl and slender features appear later in childhood, thrombotic CNS events mainly with dystonia
6-PTS deficient PKU	Myclonus, bradykinesia, rigidity, cardiopulmonary disturbances leading to ICU admissions in early infancy
Non-ketotic hyperglycinemia	Severely hypotonic newborn with CNS anomalies and myoclonic seizures
Methylmalonic academia	Two thirds present neonatally with devastating metabolic disease with ketoacidosis and hyperammonaemia; spastic infant
Proprionic academia	Nearly 90 per cent present neonatally similar to methylmalonic academia, except severe hypotonia and thrombocytopenia are hallmarks of the disease
Biotinidase deficiency	Nearly half will present with early infantile myloclonic seizures; early infantile loss of hair, eyebrows and eyelashes with dermatitis
Canavan's disease	Early infantile macrocephalic leukodystrophy with severe pyramidal tract signs and blindness

TABLE II - ALERTING SIGNS FOR COMMON GENETIC METABOLIC DISEASES	
Disease	**Alerting sign**
Fatty acid oxidation defects	Hypoglycaemia without appreciable acidosis; some types are associated with cardiomyopathy, and liver enlargement
3-methylglutaconic aciduria	Severe early infantile pyramidal or extrapyramidal tract disease, and in some neonatal severe hypoglycemia with lactic acidosis; subtle dysmorphic findings
HMG CoA lyase deficiency	75 per cent appear within first two days of life with devastating hypoglycemia and lactic acidosis but with no ketone in the urine
Pyruvate carboxylase deficiency	Severe and persistent lactic acidosis with mild or no hypoglycaemia, few if any CNS dysmorphia or symptoms
Glutaric aciduria type I	Appears at 3-8 months after a catabolic event such as diarrhoea or infections with dystonia and chorea in a macrocephalic infant; MRI reveals wide opercular sign
Isovaleric academia	Similar in appearance to methylmalonic academia with sweaty feet odour during the attack, spastic infant with marked thrombocytopenia
*** The physician must include these unusual disorders in his diagnostic considerations.**	

TABLE III - Therapeutic Modalities11,12	
Disease	**Alerting sign**
Glycogen storage disease type I	Nocturnal feeding of slowly digested glucose polymer; avoidance of fructose in severe cases
Fructose -1,6-diphosphatase deficiency	Avoidance of fructose or sucrose containing food, antibiotic or antipyretic solutions
Glycogen storage disease type 3	Similar to type 1, experimental use of alanine to prevent the appearance of cardiomyopathy
Galactosemia	Galactose free milk
Maple syrup urine disease	Branched chain restricted milk formulas
Classic PKU	Phenylalanine restricted formulas and food
Homocystinuria	Low protein or methionine restricted diet, betaine, folic acid, aspirin and in responsive variants, pyridoxine
6-PTS deficient PKU	Tetrahydrobiopterin, neurotransmitter precursors as DOPA and 5-hydroxytrtyptophan with carbi-DOPA
Non-ketotic hyperglycinaemia	High doses of dextrometorphan and sodium benzoate
Methylmalonic acidaemia	Insoleucine, and valine restricted diet, and intranasal or IM injections of hydroxycobalamin, alkalinizing citrate solutions, L-carnitine
Propionic acidaemia	Isoleucine and valine restricted diet; avoidance of fasting, L-carnitine, alkalinizing solutions of citrate
Biotinidase deficiency	Biotin
Fatty acid oxidation defects	Frequent high carbohydrate feedings, L-carnitine

TABLE III - Therapeutic Modalities11,12	
Disease	**Alerting sign**
HMG CoA lyase deficiency	Leucine restricted, low fat high carbohydrate diet, alkalinizing solutions (citrate; bicarbonate), L-carnitine
Pyruvate carboxylase deficiency	Biotin should be tried in all patients since some will respond favourably
Glutaric aciduria type I	Riboflavin, L-carbitine, baclophene, lysine restricted diet
Isovaleric academia	Leucine restricted or low protein diet, L-carnitine, and alkalinizing solutions

PRACTICAL POINTS	
1.	The Middle Eastern culture is heavily consanguineous. Inherited genetic disorders are quite common; especially inherited metabolic disorders
2.	The practicing physician must be aware of these disorders, especially those which present in the neonatal period or the first year of life.
3.	The awareness of these disorders is important to facilitate early diagnosis and initiation of treatment especially in cases of organic acidurias and aminoacidemias, to prevent neurologic crippling, and in lysosomal storage disorders to initiate bone marrow transplantation or enzyme treatment, which is preferably done in the first year of life, to prevent the progression of the disease.
4.	As treatment is either difficult and expensive or unavailable. Prevention of these disorders by premarital genetics screening (eg. Sickle cell anaemia and thalassaemia). Neonatal screening eg. Organic acidemias, aminoacidemias and pre-implantation genetics diagnosis11, if the exact molecular defect is known in any of these disorders and last but not least prenatal diagnosis and abortion, if this can be done before 120 days of conception (134 days from last menstrual period) if the disorder is incompatible with life, according to the recommendations of our Islamic leaders.