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REVIEW ARTICLE

Prevalence of neurometabolic diseases in Saudi Arabia

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ABSTRACT

Neurometabolic disorders are most often seen in newborns and infants and have come to be recognized as an important group of disorders. Understanding diagnostic and therapeutic developments in neurometabolic disorders requires a concrete understanding of the classical principles of inborn errors of metabolism in order to provide key constructs for a fundamental understanding of this interesting category of disorders. The Saudi Arabian population has a comparatively high incidence of neurometabolic disorders, primarily due to consanguinity (with a high inbreeding coefficient factor) and large family sizes. The most frequently occurring group of disorders are lysosomal storage diseases, followed by organic acidemias; intellectual disability and cerebral palsy are the most commonly presented neurological features among Saudi Arabian children. This review summarizes the reports and studies of neurometabolic disorders prevalent in Saudi Arabia. It presents an overview of the types of disorders, current screening and diagnostic strategies, and prevalence of disease conditions in Saudi Arabia.

Keywords: Neurometabolism, neurogenetics, Saudi Arabia.

Introduction

Neurometabolic disorders comprise an extensive array of diseases generally seen in newborns and infants. Seizures are common in neurometabolic disorders and they are mostly drug-resistant. Neurometabolic disorders are relatively rare but engender a substantial clinical burden. Defects or mutations in a single gene may affect the structure and function of an enzyme, resulting in an extreme neurometabolic disease. These diseases can be difficult to diagnose and treat, as some infants may have identical mutations but may not present the same neurometabolic issues; some children are severely ill at birth and die shortly after the symptoms have been identified, while others may be only slightly affected or have clinical signs that are presented later in life (1).

A number of studies have been published over the past two decades in relation to the incidence of different neurometabolic disorders in Saudi Arabia. The estimated general frequency of neurometabolic disorders in Saudi Arabia is approximately 1:635, which is exceedingly higher than that in any other country (2,3). Newborn screening (NBS) data indicate that the overall incidence of inborn errors of metabolism (IEM) disorders in the Saudi Arabian population is approximately 1:1,443, with propionic acidemia (PA, 1:1,400) being the most common (4). This is a much higher frequency than that in other countries, such as in the USA the reported incidence of PA is approximately 1:1,792 (5). Saudi Arabia has a comparatively high rate of consanguineous marriages (approximately 60%) (6), much higher than that in Canada, the USA, Japan, and Southern Europe. In a study on the global prevalence of IEMs in children, which included studies published from 1980 to 2017 (7), the global IEM frequency was estimated to be 50.9 per 100,000 live births (95% CI = 43.4–58.4). On the contrary, the highest rate observed in the Eastern Mediterranean region was 75.7 per 100,000 live births (95% CI = 50.0–101.4), which could be due to high parental consanguinity in the region.

A retrospective review of children diagnosed with IEMs in Saudi Arabia conducted over 13 years (8) had detailed various clinical and biochemical investigations carried out for IEM diagnosis, which primarily analyzes the levels of ammonia, ceruloplasmin, plasma amino acids, urine organic acids, very-long-chain fatty acids, carbohydrate-deficient transfer, and total homocysteine as well as quantification of polyols and lactic acid in the urine. The review also reported that of 110,601 births in the region, 187 were

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diagnosed with an IEM – an incidence of 169 cases per 100,000 births. In addition, out of these 187 IEM patients, 64.7% and 35.3% had a small molecule or a large molecule disease, respectively (8). The major categories of small molecule diseases included citrullinemia, inborn errors of carbohydrates, aminoacidopathies, organic acidemias, vitamin responsive disorders, and fatty acid oxidation defects. Large molecule diseases included lysosomal storage diseases (LSDs), sphingolipidosis, mucopolysaccharidosis (MPS), glycogen storage diseases, peroxisomal disorders, and congenital disorders of glycosylation (CDG). In complex molecule disorders, LSDs were the most common form. Organic acidemias were the most common in the small molecule disorder group. In Saudi Arabia, MPS VI is the most common type of MPS (8).

A significant disparity has been noted in the prevalence of genetic diseases in Saudi Arabia compared to other parts of the world (6,8). Obaid et al. reported that patients with very-long-chain acyl-CoA dehydrogenase deficiency (VLCADD) had novel missense mutations in exon two that resulted in early death (9). The observed results corroborated the previous reports published by Al-Owain et al. (10), which showed that the observed number of private mutations was almost double than that of founder mutations in patients with VLCADD.

These results were supported by another study examining the occurrence of IEMs in the Eastern Province of Saudi Arabia from 1983 to 2008 (2). In that study, the patients were categorized into different groups: small-molecule disorders (urea cycle defects, aminoacidemia, organic acidopathies, fatty acid oxidation, and carbohydrate metabolic disorders) and other disorders (LSDs, glycogen disorders, and organelle disorders), based on the accumulation or deficiency of metabolites. It was estimated that approximately 165,530 Saudi Arabian infants were born at Saudi Aramco during the study period, of which 248 were diagnosed with an IEM, (i.e., a cumulative incidence of approximately 150 cases per 100,000 live births). It was observed that the most frequently occurring disorder was LSD, with an incidence of 1:2236 and accounting for 31.3% of all IEM diagnoses (45 cases per 100,000 live births). This incidence of LSDs in Saudi Arabia is much higher than that reported globally (1:7,100–7,700) (2,6,7,11–14). The incidence of MPS was 7% (16.9 cases per100,000 live births), with the most common being MPS VI, which was also higher than that reported in other countries (7). Among the small molecule disorders, a higher incidence of organic acidopathies (1:3,448) was observed in the Saudi Arabian population than in other countries, and the incidence of fatty acid oxidation disorders was rather lower (1:82,765) than that of other disorders. Furthermore, it is worth noting that LSDs are not yet part of the NBS program in Saudi Arabia and, therefore, are not included in the assessments of the rate of IEMs in Saudi Arabia. This review provides an outline of the most promising reports of different neurometabolic disorders (detailed in Table 1) in Saudi Arabia.

Method

For this review, a literature search was conducted using PubMed to search for all relevant articles, without specific time limitations, but with a focus on literature published within the last 5–10 years. The literature related to the different categories of IEM disorders was searched, with interest in research related to Saudi Arabia. The keywords included all IEM disorders and categories of disorders in conjunction with the word "Saudi Arabia" to support identifying the research literature related to the specific geographic location of interest. In addition, articles related to IEM disorder prevalence in general or in geographic areas outside Saudi Arabia were included to compare the incidence of different disorders and their pathogenic variants. Overall, approximately 50 articles were reviewed. One of the aims of this review is to compare and contrast the different IEM disorders in Saudi Arabia and in other locations worldwide. Unfortunately, there was a lack of interventional studies, or randomized control trials, with the research demonstrating primarily retrospective descriptive studies. The available research literature found as part of the review is cited and discussed in this review. The review and discussion of the extant literature are classified into categories of IEM disorders.

Review of the Literature on IEM Disorders

Amino acid disorders

Reports on the incidence of phenylketonuria (PKU) in Arab countries have been published over different periods with differing results. In one study, 7 of 138,718 (0.0050%) patients were found to have PKU (15), while in another study 51 of 750,365 (0.0068%) were diagnosed with PKU (16). A global comparison that included countries with national NBS programs showed that Japan had the lowest incidence rate of PKU (1:125,000, 0.0008%) among Asian countries, followed by China (1:17,000, 0.006%), where the rate is similar to that of Saudi Arabia (16). The incidence of PKU in the UAE (1:12,369, 0.008%) is also similar to that in Saudi Arabia (17).

Classical PKU is rare in Saudi Arabia, where 6-pyruvoyl-tetrahydropterin synthase deficiency is the most common cause of hyperphenylalaninemia. Hyperphenylalaninemia can be caused by tetrahydrobiopterin deficiency, which is most often a result of a deficiency in 6-pyruvoyl-tetrahydropterin synthase, an enzyme that catalyzes the second step of de novo tetrahydrobiopterin synthesis (17).

Organic acid disorders

Organic acid disorders are the second most common group of small molecule disorders, second only to LSDs (18). The incidence of PA is reported to be between 1:50,000 and 1:100,000 worldwide, and it is the most frequently encountered organic aciduria. PA is considered to be predominant in NBS in Saudi Arabia, with an approximate incidence of 1:12,500 live births (4). Reports suggest that

Table 1. *Types of neurometabolic disorders.*

Group	Subtypes	Characteristics of specific disorders	Worldwide prevalence	Prevalence in Saudi Arabia	Founder mutation	Reference
LSDs	• Tay-Sachs • Fabry (male and female) • Gaucher Disease • Farber Disease • Sandhoff Disease • Niemann-Pick A/B • Niemann-Pick C • MPS I • MPS II • MPS III B • MPS III C • MPS IVA (most common)	Accumulation of normally degraded substrates within lysosomes leading to multi-organ failure.	1:7,100–7,700	37:100,000	Multiple sulfatase deficiency *SUMF1* c. 785 A>G (46)	(18) (26) (35) (38) (39)
Amino acidopathies	• PKU • Maple Syrup Urine Disease • Homocystinuria/Methylene Tetrahydrofolate Reductase deficiency	Impaired proteins or enzymes production.	China:1:17,000 Japan at 1:14,623	27:100,000	PTPS: c.238A>G; p.M80V. (48)	(9) (18) (22) (23) (24) (32)
Organic acidopathies	• PA • methyl malonic acidurias (MMA) • branched chain organic aciduriaas (which includes isovaleric aciduria)	Defect in intermediary metabolic pathways of carbohydrate, amino acids, and fatty acid oxidation. Leads to accumulation of organic acids in tissues and their subsequent excretion in urine.	1:50,000 to 1:100,000	30:100,000	PA: (c.425G>A; p. Gly142Asp) in *PCCA*. MMA c.329 A > G(p. Tyr110Cys)	(18) (25) (26)
Urea cycle disorders	• N-acetylglutamate synthase deficiency • Argininosuccinic aciduria • Ornithine transcarbamylase deficiency • Carbamoyl phosphate synthetase I deficiency	Deficiency in specific enzymes needed to break down amino acids or other metabolites thereby allowing them to accumulate and become toxic if not treated.	1:350,000	11:100,000		(18) (27) (28)
Fatty acid oxidation defects	• VLCADD • Trifunctional protein deficiency • Long-chain 3-hydroxy acyl-CoA dehydrogenase deficiency • Multiple acyl-CoA dehydrogenase deficiency	Occurs due to disruption of either mitochondrial β-oxidation or the fatty acid Transport using the carnitine transport pathway.	1:100,000 and 1:120,000 live births (22) (49)	1:37,000	*ACADVL* c.65C>A;p. Ser22X. (25) *ACADM* c.362C>T (24).	(3) (40)

continued

Group	Subtypes	Characteristics of specific disorders	Worldwide prevalence	Prevalence in Saudi Arabia	Founder mutation	Reference
Neurotransmitter disorders	• Aromatic amino acid decarboxylase and tyrosine hydroxylase deficiency • Pyridoxine-dependent seizures • Biotin–Thiamine-Responsive Basal Ganglia Disease	Characterized by disturbances of neurotransmitter metabolism.			BTRBGD: c.1264A> G (p. Thr422Ala) (18).	
Peroxisomal disorders	• Zellweger syndrome • Rhizomelic chondrodysplasia punctata • Neonatal adrenoleukodystrophy	Results due to impairment in one or more peroxisomal functions.		1:30,000		(41)
Congenital disorders of glycosylation	• Congenital disorders of N-linked glycosylation • Congenital disorders of O-linked glycosylation • Mixed glycosylation disorder	Caused by defects in the synthesis and processing of the asparagine-linked oligosaccharides of glycoproteins.		11.5:10,000		(13)
Mitochondrial disorders	• Myopathy, encephalopathy, lactic acidosis, and stroke-like episodes • ISCA2	Related to abnormalities of oxidative phosphorylation.			ISCA2; c.229G > A, p.Gly77Ser	(42)
Glycogen storage disorders	• Von Gierke disease • Pompe disease • Andersen's disease • McArdle's disease	Associated with altered glucose metabolism and breakdown leading to hypoglycemia/ hepatomegaly				(29)

the frequency of PA in some tribes of Saudi Arabia is even higher, in the range of 1:2,000–1:5,000 (3). In PA, seizures can be easily controlled, but there is no clear relationship between genotype and phenotype (4). In 2019, Al-Hamed et al. (19) reported a cohort of 84 patients from 84 families in which pathogenic *PCCA* variants were the most specific molecular genetic cause of PA. In the entire Saudi Arabian population, the c.425G>A (p.Gly142Asp) variant was the most common founder variant causing PA.

Urea cycle disorder

The prevalence of urea cycle disorders is estimated to be 1:350,000 worldwide, although this may be an underestimation. The incidence of urea cycle disorders may have significant geographical variations, as these disorders are more common among French Canadian and Japanese populations (20). In regions of Saudi Arabia, the incidence of the urea cycle disorder citrullinemia was found to be 1:17,222 (21).

Fatty acid oxidation disorders

The molecular, clinical, and biochemical characteristics of VLCADD in Saudi Arabia, as with the available treatment modalities and relevant outcomes, were reported in a retrospective analysis that encompassed 14 years and included 37 patients with VLCADD (9). The patients in the study were detected in NBS by tandem mass spectrometry (22,23), and subsequently treated with a metabolic formulation containing medium-chain triglycerides (MCT) and carnitine supplementation, monitored, and followed up (9). MCT diffuses directly into the mitochondria and helps to bypass the related enzyme deficiency, while carnitine supplementation helps eliminate the accumulated organic acid metabolites. Homozygosity for a c.65C > A nonsense mutation was the most common in the cohort, noted among 83.7% of the patients (9). The outcome of the disorder in the population of Saudi Arabia was poor, despite diagnosis and available treatment opportunities. As with other IEMs, the most probable explanation for the relatively high incidence of VLCADD is the high rate of consanguinity in the Saudi Arabian population.

In patients with medium-chain acyl-CoA dehydrogenase disorders, the most common genetic variant in western countries is c.985A > G, but in Saudi Arabia it is c.362C > T (24). Oxidation of fatty acids involves a mitochondrial enzyme, short-chain enoyl-CoA hydratase (SCEH), and SCEH deficiency, leading to the early childhood disorder Leigh syndrome. Obaid et al. presented cases of severe refractory lactic acidosis that resulted in death within the first two days of life (9). They also carried out an autozygome/exome analysis and the same homozygous splice site mutation was observed in both cases, a homozygous nonsense mutation in exon two of ACADVL c.65C>A;p. Ser22X. They suggested that the death of these patients was due to an accumulation of toxic intermediate metabolites, which could have caused brain toxicity (9).

Lysosomal storage diseases (LSDs)

LSDs are the most common groups of IEMs in Saudi Arabia (17,18). The reported prevalence of LSDs in Saudi Arabia and the incidence of neuronal ceroid lipofuscinosis (NCL), multiple sulfatase deficiency (MSD), and Morquio disease were notably higher in the Saudi Arabian region (6,25–28) compared to the worldwide prevalence of LSDs (1 in 7,100–7,700 live births; 27). In more than 50 individual LSDs, Gaucher disease is the most common, representing 14% of all LSD cases, followed by MPS I, metachromatic leukodystrophy, MPS IIIA, and Fabry disease, representing 7% of all LSD cases at an incidence of 0.1–0.9 per 100,000 persons (26). Pompe disease accounts for 5% of all LSDs, and one-third of the cases are infants (29). The prevalence of Pompe disease was estimated to be between 1 per 14,000 infants in China and Taiwan and 1 per 138,000 infants in the Netherlands (27,29,30), and the overall prevalence ranges between 0.1 and 2.7 per 100,000 persons (27–31).

Al-Gazali et al. reported on a group of patients with MSD, also referred to as Austin disease, caused by a novel homozygous missense mutation in *SUMF1* (NM 182760.3; c.785 > G [p. Gln262Arg]) (32). The patients had specific symptoms related to developmental impairment, intellectual disability, ichthyosis, and white matter periventricular disease. The disorder was more pronounced in the classical juvenile form of MSD but less evident than in the conventional childhood-onset form of MSD. The differential expression of MSD may be due to the unusual pathogenic mechanisms rather than the amount of residual activity (32).

Peroxisomal disorders

Peroxisomal disorders are known to be very rare and the number of large cohorts that feature the biochemical, molecular, and phenotypic features of these disorders are extremely limited. In a study conducted by the National Health Service, the largest Arab cohort studied included 72 families with clinically, biochemically, and molecularly characterized patients with peroxisomal disorders (31,33). The most commonly mutated gene in patients with peroxisomal disorders is *PEX1* (22%), followed by *HSD17B4* (21%). The disease prevalence was 1:30,000, which was found to be higher than the previous levels in other demographics (31). As with other IEMs, the major causes of the increased incidence of peroxisomal disorders in Saudi Arabia are the high rate of consanguinity and large family size.

Neurotransmitter disorders

Neurotransmitter disorders have diverse genetic causes that result in different epilepsies. In a retrospective study involving a series of patients diagnosed with early infantile epileptic encephalopathies (34), the diagnoses were further confirmed by laboratory molecular investigations. The neurotransmitter disorder in this patient group was due to mutations in genes responsible

for synapsis, neurotransmitters, and receptors (*AP3B2, FRRS1L, GRIN2B*), ion channels (*KCNB1*, *SCN1A*), signal transduction (*ARHGEF9, GNA01*), and organelles and cell membranes (*ARV1, PCDH19*) (35). These results confirmed that higher rates of neurotransmitter disease could be attributed to a predominance of autosomal recessive genotypes resulting from consanguineous marriage (34).

Biotin–thiamine-responsive basal ganglia disease, caused by defects in *SLC19A3*, has wide variability in phenotypes and the age of onset (36), but it is mainly characterized by intractable seizures following stress (e.g., trauma and fever). Biotin–thiamine-responsive basal ganglia disease is caused by a defect in a thiamin transporter (hTHTR2), and there is potential that early intervention with thiamine and biotin can ameliorate the clinical phenotype and help with seizure control. On the whole, 52% of the reported cases of this disorder are from Saudi Arabia, where the estimated carrier frequency is 1:500 (4,36).

The prevalence of pyridoxine-dependent epilepsy (PDE) is unknown, but estimates vary from 1:20,000 infants with epileptic encephalopathy to 1:600,000 in the UK (34). Because the underlying cause of the genetic defect of PDE was unknown for a long time, the diagnostic criteria were limited and diagnosis may have been missed in many cases.

Congenital disorder of glycosylation (CDG)

In addition to other organ systems, CDG primarily involves the central nervous system. In a retrospective study involving 27 patients with CDG from Saudi Arabian hospitals, Alshenaifi et al. concluded that the application of next-generation sequencing and the fundamentals of glycobiology have broadened the scope of CDGs, opening up new avenues for understanding individual types of CDGs as well as the associated underlying mechanisms of different pathways (33). Well-known CDGs are inherited in an autosomal recessive manner and have substantial defects in the N-glycan assembly. Molecular studies have shown that all the 27 patients with CDG had homozygous mutations in ALG3-CDG (26%), ALG9-CDG (29.5%), MGAT2-CDG (11%), and/or COG6-CDG (26%) (37). In this cohort, the combined carrier frequency of CDG was 11.5 cases per 10,000 people. This research provided valuable epidemiological data on the prevalence of CDGs in a large patient cohort (33,37).

Conclusion

Recent studies on genetics in the Saudi Arabian population have contributed significantly to the global effort to track the causal mutations of diseases with Mendelian inheritance patterns, especially in the field of autosomal recessive diseases. Consanguinity and large family size are the two most dominant contributors to the prevalence of recessive congenital diseases among the Saudi Arabian population. Irrespective of the availability of a plethora of data published on the prevalence of different genetic diseases in Saudi Arabia, there is still a major gap in mapping the distribution of these diseases and their genetic landscape. The emergence of enhanced NBS for treatable metabolic disorders has significantly improved the rate of early diagnosis, expanded management, and improved outcomes for many patients. Nevertheless, the treatment and prognosis of some untreated epilepsy-causing metabolic disorders, such as peroxisomal and mitochondrial disorders, have not improved dramatically over the last few decades despite advances in technology and testing. However, the advent of novel technologies and the continuous efforts of researchers have raised the expectations for continued improvement in the near future.

Future Directions

Further research is needed to delineate specific aspects of the incidence of different, but related, neurometabolic disorders. For example, limited awareness of available treatments for seizures related to PDE and antiquitin deficiency means that this disorder likely remains significantly underdiagnosed. The literature is lacking in interventional studies and randomized control trials. Research in this area is limited because these disorders are so rare; thus, information and collaboration are necessary to support continued treatment advancements.

Despite the availability of data on different genetic diseases in Saudi Arabia, there is a gap in mapping the distribution of these diseases and their genetic landscape; therefore, additional research is needed. In addition, information on metabolic diseases with unknown prevalence or inadequate prevalence is also needed. To conclude, little research is available on the new genetic tools for diagnosing and treating these disorders, which therefore requires further investigation.

List of Abbreviations

CDG	congenital disorders of glycosylation
IEM	Inborn error of metabolism
LSD	lysosomal storage disease
MCT	medium-chain triglycerides
MPS	mucopolysaccharidosis
MSD	multiple sulfatase
NBS	newborn screening
NCL	neuronal ceroid lipofuscinosis
PA	propionic acidemia
PDE	pyridoxine dependent epilepsy
PKU	phenylketonuria
SCEH	short-chain enoyl-CoA hydratase
VLCADD	very-long-chain acyl-CoA dehydrogenase deficiency

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