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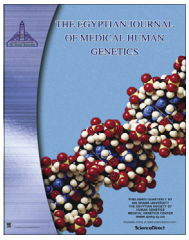

CASE REPORT

Challenges in diagnosis and counseling of a family with two recessive neurometabolic disorders

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Abstract Neurometabolic disorders are a group of inborn errors of metabolism where neurological symptoms predominate especially convulsions which are usually resistant to antiepileptic drugs. Other symptoms include poor feeding, vomiting, lethargy, seizures, and loss of consciousness. Because of the nonspecific overlapping symptoms, confirming the diagnosis depends mainly on the specific investigation that is done in highly specialized laboratories.

The clinical picture can be more complicated in the presence of two diseases in the same family and more difficult if present in the same patient. This is not extremely rare in countries with high prevalence of consanguineous marriage like Egypt. The situation is more complicated when we add the lack of specific investigations, metabolic specialized labs and the deficiency of documentation.

In this case report, we present the challenges that we met in diagnosis and counseling of a family with both Tay–Sachs and maple syrup urine disease depending mainly on history, clinical data and a few diagnostic investigations.

1. Introduction

Inborn errors of metabolism (IEM) result from the lack of activity of one or more specific enzymes or defects in the transportation of proteins that result in the accumulation of substances usually present in small amounts, the deficiency of critical intermediary products, the deficiency of specific final products or furthermore the noxious excess of products of alternative metabolic pathways [1].

Maple syrup urine disease (MSUD) is an autosomal recessive disease associated with defects in the branched chain α ketoacid dehydrogenase complex (BCKD) resulting in a buildup of branched chain amino acids which are neurotoxic that cause swelling of the white matter causing lethargy, reduced muscle tone, and convulsions [2]. MSUD is divided into four major categories of classic, intermediate, intermittent, and thiamine responsive [3].

The G_{M2}-gangliosidoses is considered a heterogeneous group of disorders resulting from a failure in lysosomal hydrolysis of G_{M2}-ganglioside; due to a primary deficiency of the β-hexosaminidase A (β-hex A) enzyme or its cofactor (the G_{M2}activator protein) [4]. The classic infantile form (Tay–Sachs (TSD) or Sandoff disease) is characterized by the onset at 4–8 months and progressive neurological deterioration with macular cherry-red spots, blindness, intractable seizures and paralysis. Late onset Tay–Sachs disease is characterized by progressive spasticity and rigidity, convulsion and dementia that have its onset in childhood or later [5]. It is classified into juvenile onset form in which individuals

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ultimately enter a vegetative state between the ages of 5 and 15 years and an adult form that manifests later with cerebellar, anterior horn cell involvement and sometimes with neuropsychiatric problems [6].

Although both diseases are categorized as IEM and both have a progressive course, patients with TSD usually acquire normal milestones of development in the first 6 months of life while patients with MSUD have an acute onset of neurological symptoms in the first few days of life [5,11]. Unless proper investigations are requested, the differentiation between the two diseases is extremely difficult.

Here we report an Egyptian patient who had both MSUD and TSD and the challenges we faced in diagnosis and counseling of this family.

2. Case report

A first cousin parents were referred to the Genetics Clinic because of repeated infant deaths. They had three children (two girls and one boy) with convulsions that start a few hours after birth and failure to thrive that ended by their death after a few months. They had also a fourth child (girl) who was normal till the age of 6 month then developed hypotonia, progressive loss of previously acquired milestones of development and convulsions that also ended by her death at the age of 14 months. There was also a maternal cousin who had mental retardation and convulsions and died at the age of 4 years, Fig. 1. No diagnostic investigation was done before their death. The parents were counseled that they may probably have two recessive diseases as the onset and the course of the disease in their children is different, one of them could be TSD (being the most common disease with this presentation) with the possibility of testing them for the carrier status. Carrier testing for the mother revealed reduced leucocyte and plasma activity of Hexosaminidase A enzyme indicating a carrier status for TSD, Table 1. Genetic counseling was done with the recommendation of testing the husband and prenatal diagnosis for TSD. We also stressed upon the fact that TSD does not explain the early death of the three children with neonatal convulsions and so testing further pregnancy outcome by extended metabolic screen is also mandatory. We lost contact with the family and then they presented to the genetics clinic after one year with a three week old newborn girl suffering from poor suckling and respiratory distress. The patient was delivered at full term by cesarean section and the parents confirmed that they did prenatal diagnosis of TSD disease at nine weeks of pregnancy in another lab using enzyme assay and revealed normal result. The result of the prenatal diagnosis was not available. Extended metabolic screen was done and revealed elevation of branched-chain amino acids leucine, isoleucine and valine diagnostic of MSUD. She started treatment immediately in the form of protein restriction and special MSUD milk formula and had almost normal physical and mental development till the age of 10 months when she developed generalized tonic–clonic convulsions for which she was prescribed anticonvulsants (Sominaletta and Tiratam) with no proper control. It was also noticed that she had a gradual deterioration of vision and loss of previously acquired milestones of development. She also developed hypertonia in both upper and lower limbs with exaggerated deep tendon reflexes. Fundus examination was done and revealed bilateral pale optic disc. Diagnosis of Tay–Sachs disease was confirmed by enzymatic assay. The parents were counseled again explaining the

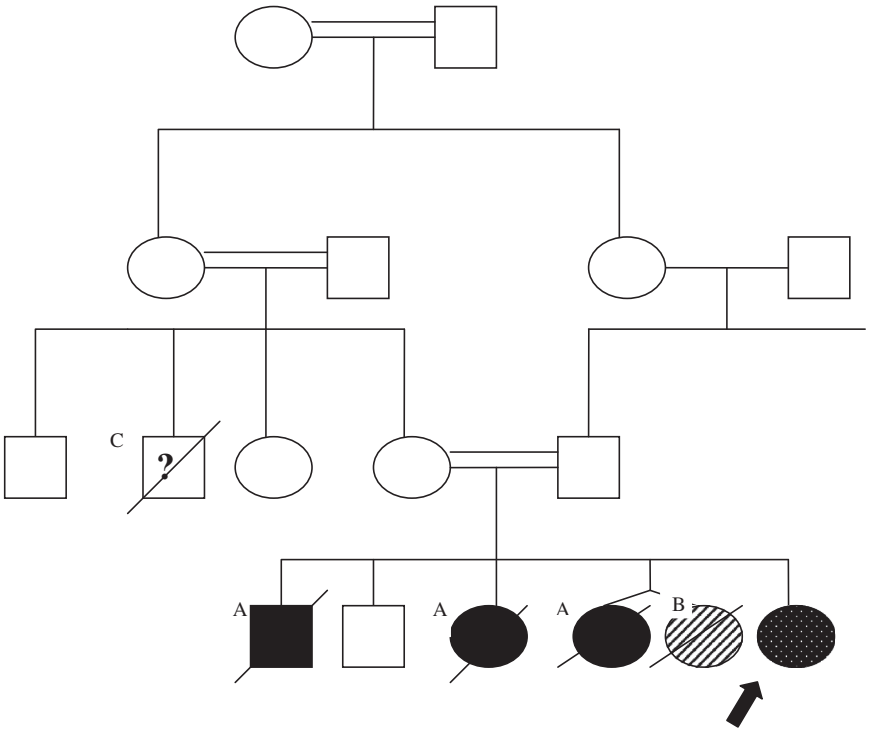

Figure 1 Family pedigree. (A) poor suckling, failure to thrive and convulsions, died at the age of 1–3 months. (B) Normal till the age of 6 month then developed hypotonia, progressive loss of previously acquired milestones of development and convulsions. (C) Mental retardation died at the age of 4 years.

Table 1 Carrier screening of Tay–Sachs disease in the mother.

	Sample	Mother	Control
Activity in leucocytes (nmoles/h/mg protein)	Total β-hexosaminidase	1114	1488
	β-Hexosaminidase A	257	874
	β-Hexosaminidase A/total	0.23	0.59
	β-Hexosaminidase A substrate specific	45	149
Activity in plasma (nmoles/h/ml protein)	Total β-hexosaminidase	928	780
	β-Hexosaminidase A substrate specific	53	76

possibility of maternal cell contamination in the CVS sample taken for diagnosis of their child. The patient was kept on the MSUD diet and the levels of branched chain amino acids were always controlled but her neurological status progressively deteriorated till her death at the age of 2 years.

3. Discussion

We report a 3 year old child with two rare recessive neurometabolic diseases with overlapping symptoms and signs that may confuse the treating physician if the family history is not carefully investigated. The occurrence of two recessive genetic diseases in the same family has been reported before and sometimes it can suggest a different diagnosis [7]. This may be attributed to the high prevalence of consanguineous marriages in Egyptian population [8].

Consanguineous mating is genetically important as closely related individuals have a higher chance of carrying the same alleles than unrelated individuals; hence the offspring of consanguineous mating are more frequently homozygous for various alleles than those from other unions [9].

The absence of medical records and lack of investigations in the deceased children is another challenge that we had to overcome and we had to search for other clues in history and clinical picture to elucidate what diseases this family might have had that led to the tragic death of three children.

MSUD is an autosomal recessive inborn error of metabolism leading to accumulation of the branched-chain amino acids (leucine, isoleucine, and valine) which are toxic to the central nervous system and can produce different grades of neuropathy, or even death, if the disease is not treated [10]. The worldwide incidence of MSUD is approximately 1 in 185, 000 live births [10] while the prevalence in our clinic (the largest clinic for IEM in Egypt) is 13.4% of all patients with IEM [personal communication]. Onset of the disease is usually after a few days of birth [11]. This is in contrast to GM2 in which the child is normal for a longer period ranging from 4 to 8 months and then progressively have neurological deterioration with macular cherry-red spots, blindness, intractable seizures and paralysis [5]. This difference of onset was the most important clue in family history that indicated the presence of two different diseases in the same family.

Hexosaminidase A enzymatic activity is the primary method of population screening and carrier detection of TSD disease because of its greater sensitivity compared to targeted mutation analysis [12].

Being a country with limited medical and financial resources, searching of the other disease in the family using molecular testing was not applicable or cost effective and so genetic counseling explaining the importance of selective newborn screening in the next pregnancy was done.

Selective screening is carried out in neonates and children who develop symptoms or have family history indicative of an IEM [13]. There are a few Arab countries in the Middle East and North Africa region that have started a newborn screening (NBS) program, while others have either a limited hospital-based selective NBS program or have just completed pilot studies [14–16]. Recently, Egypt has recently started a newborn screening for only PKU and hypothyroidism.

Neonatal screening and sophisticated enteral and parenteral treatment protocols have significantly improved neurological outcome in patients with classic MSUD but risks of acute brain injury or death are always present and the long-term neuropsychiatric prognosis is guarded [10,17].

Our patient had gradual deterioration of vision and started to loose previously acquired milestones of development in spite of good metabolic control of MSUD evidenced by repeatedly optimal plasma levels of branched chain amino acids. This should direct the treating physician to search for another disease, like TSD in this family.

TSD occurs at high frequency in Ashkenazi Jewish individuals due to a shared genetic background, with an incidence of 1 in 2500 to 3900 live births compared to 1 in 320,000 in the general population [18]. Following the development of prenatal diagnosis for TSD in the early 1970's [19], most couples who had had an affected child chose to monitor subsequent pregnancies and bring to term only pregnancies of unaffected fetuses as the parents of our patient did. However, Chorionic villus sampling (CVS) has been performed at 9 menstrual weeks for the prenatal enzymatic diagnosis of TSD and revealed normal enzymatic assay. This could be explained by maternal cell contamination [20] which should always be excluded by microsatellite analysis in all samples of prenatal testing and that was not done to the current patient.

4. To conclude

The occurrence of two recessive diseases in the same patient is not rare in the Egyptian population due to the high prevalence of consanguineous marriage. This may complicate the clinical picture, the diagnosis and management. Reaching an accurate diagnosis is of utmost importance for proper genetic counseling and family planning.

Conflict of interest

The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

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