Case report

Zellweger syndrome

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Introduction

Zellweger syndrome, also known as "cerebro-hepato-renal syndrome" is the most severe and common peroxisomal disorder which presents in the neonatal period with multisystem involvement[1]. It is a rare inherited disorder and estimated incidence is 1 in 50 000 to 100000 live births[1]. We present the first reported case of Zellweger syndrome in Sri Lanka.

Case report

A 10-month-old male child with global developmental delay, seizures and facial dysmorphism was admitted to the neurology unit for further evaluation and management. He was the only child of second degree consanguineous parents with unremarkable family history of neurological disorder. His antenatal and perinatal periods were uncomplicated except for a transient period of poor sucking and lethargy. Since birth, he exhibited significant developmental delay and at 10 months of age his development age was 6/52. He had been having myoclonic seizures from 6/52 of age.

His growth parameters were well below the third centile and he exhibited distinctive facial features including flat face, high forehead, wide anterior fontanelle, broad nasal bridge, micrognathia, high arched palate and flat occiput. He had nystagmoid eye movement and significant hypotonia with reduced reflexes. Systemic examination revealed hepatomegaly.

A clinical diagnosis of Zellweger syndrome was made and further supported by presence of bilateral profound sensorineural deafness, renal cyst, acetabular dysplasia, gross EEG (electro encephalogram) abnormality (Figure 1) and cerebral hypomyelination. Elevated blood levels of very long chain fatty acids confirmed the diagnosis (Table 1).

Table 1. Plasma – very long chain fatty acid

	Patient results ugm/ml	Normal controls ugm/ml	Zellwager ugm/ml
C26:0	1.43	0.23+/-0.09	1.0+/-1.5
C24/C22	0.73	0.84+/-0.10	2.07+/-0.28
C26/C22	0.21	0.01+/-0.004	0.5+/-0.16

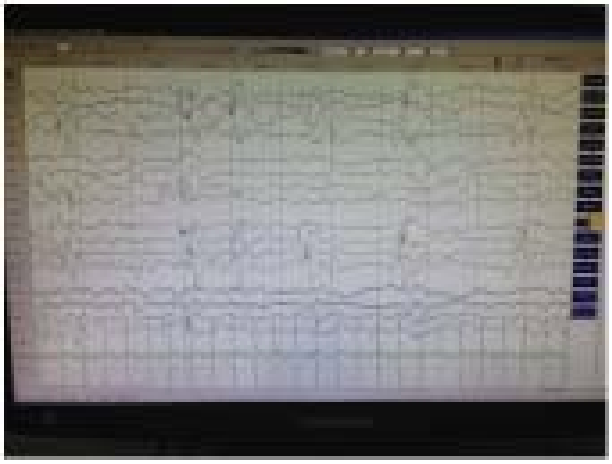

Figure 1. EEG showing poorly formed background with multifocal epileptiform activity

Discussion

Zellweger syndrome was first described in 1964 by Ulrich Zellweger a Swiss-American professor of pediatrics and genetics[2]. Itis the most severe form of peroxisome biogenesis disorders (PBDs) which are characterized by the failure of the body to produce functional peroxisomes which play a vital role in numerous biochemical processes in the body, especially in the beta oxidation of very long chain fatty acids (VLCFAs)[1,3]. Peroxisomal dysfunction and the resultant derangement in metabolism result in a multisystem disorder which mainly affects the brain, liver and kidneys. Zellweger syndrome is a lethal disease and survival beyond one year is unusual. Diagnosis could be made based on clinical, biochemical, radiological, histological and genetic studies.

Characteristic dysmorphism of Zellweger syndrome includes flat face, high forehead, large fontanelles, broad nasal bridge, small nose with anteverted nares, micrognathia, high arched palate, extra folds of skin on the neck, shallow bony ridges of the eye socket and flat occiput[1]. They develop a spectrum of neurological complications: frequent seizures, profound hypotonia, poor or absent reflexes, mental retardation and developmental delay. Among them profound hypotonia is characteristic and acts as a guide towards the diagnosis[3]. In addition, diagnosis is supported by a variety of eye abnormalities

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(hyperteleorism, cataracts, corneal opacities, optic atrophy, nystagmus, glaucoma) hearing loss, splenomegaly and hepatomegaly[1]. Minor skeletal abnormalities like clubfoot and camptodactyly and certain heart defects such as septal defects and patent ductus arteriosus have been reported[1]. Our patient had many of these clinical features which assisted us in the diagnosis.

Radiological evaluation gives further supportive evidences to arrive at the diagnosis. Neuronal migration defects and cerebral hypomyelination are highly suggestive of Zellweger syndrome[1,3]. For example, all the 6 Zellweger syndrome cases reported by James and Wallace (1997) had impaired myelination, diffusely abnormal cortical gyral patterns and germinolytic cysts in the caudothalamic groove[4]. X ray can be used to identify characteristic chondrodysplasia punctata and acetabular dysplasia[1,3]. In addition, routine abdominal ultrasound shows renal cysts in 70% of cases[5]. The radiological features seen in our patient were acetabular dysplasia, isolated renal cyst and cerebral hypomyelination.

Microscopic evidence of reduction in number of peroxisomes on hepatic and renal biopsy helps to arrive at the diagnosis[6]. However, the most commonly used and most informative initial screen test is the measurement of VLCFA concentrations in plasma[7]. Elevation of C26:0 and C26:1 and the ratios C24/C22 and C26/C22 are consistent with a defect in peroxisomal fatty acid[3].

Definitive diagnosis is based on genetic studies. Zellweger syndrome is an autosomal recessive disorder that is caused by mutation in anyone of 13 genes, termed PEX genes that encode peroxins which are proteins required for the normal peroxisome assembly. A majority of the patients exhibit either a mutation in PEX1 or PEX6[3] gene. We were not able to perform genetic studies in the described patient due to limited access and cost factors.

Conclusion

Etiological diagnosis of development delay is a tedious process as the differential diagnosis is extremely wide. Diagnosis is important for possible therapeutic intervention and genetic counselling. Careful clinical evaluation will help in directing investigations. Characteristic facial appearance, profound hypotonia, nystagmoid eye movements and hepatomegaly of described patient point towards the diagnosis of Zellweger spectrum disorder.

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