Zellweger Syndrome: A Case Report


Abstract

Zellweger syndrome, an autosomal recessive disorder, is generally considered as the prototype of the group of the rare peroxisomal disorders. Infants with Zellweger syndrome have a striking constellation of clinical features, which usually suggests the diagnosis. The condition has been reported in all races and from all parts of the world. Considerable progress has been made recently in the biochemical and molecular aspects of the disease as well as identifying the genetic defects involved. Here we present a case of Zellweger syndrome and discuss the pathophysiology of the disease. To our knowledge, this is the first case of Zellweger syndrome reported from United Arab Emirates.

Key words: Zellweger syndrome, peroxisomal disorders, hypotonia, neonatal convulsions.

Case report

A full term female baby weighing 3000g was born in Mafraq Hospital, Abu Dhabi, United Arab Emirates, by spontaneous vaginal delivery to a primigravida mother who did not have any specific medical problems during antenatal period and had not received any medications. The parents were first cousins. There was no family history of any inherited disorders. Baby was hypotonic at birth and needed resuscitation for a few minutes with bag and mask ventilation. She continued to remain markedly hypotonic, even though her heart rate and respiration became normal. Within the first 30 minutes after birth, she developed tonic convulsions of limbs and twitching movements of face needing intravenous phenobarbitone to control them. She was noted to have following dysmorphic features: high forehead, large anterior fontanelle, depressed nasal bridge, epicanthic folds, and receding chin (Figure 1).

Figure 1: Showing flat face, prominent forehead, thin supraorbital ridges and expression less face

The liver was palpable 2cm below the right coastal margin. Spleen and kidneys were not palpable. There was a soft systolic murmur over the precordium. Deep tendon reflexes were not elicitable. Red reflex was present in both eyes, there were no cataracts, and fundus examination was normal.


1 Department of Neonatal Medicine & Surgery, Mafraq Hospital, Abu Dhabi, United Arab Emirates
Routine laboratory investigations such as complete blood count, blood glucose, electrolytes, blood gas analysis, and renal function tests were normal. Liver function tests were within normal limits. X-ray of long bones revealed stippling calcification of patellae (Figure 2), and around shoulder and elbow joints.

The results of assay of plasma very long chain fatty acids are given in table. An ultrasound examination of kidneys did not reveal any cystic changes and auditory brain stem response was normal. CT scan brain was normal. Echocardiogram showed a small ventricular septal defect. A diagnosis of Zellweger syndrome was made and the prognosis was explained to the parents.

Course in hospital: Baby continued to remain hypotonic with very poor sucking and swallowing reflex necessitating nasogastric tube feeding. In spite of giving adequate calories and proteins, she had poor weight gain. She did not attain any developmental milestones at the age of three months, when she was sent abroad for further management at the request of the parents. Investigations at this time revealed bilateral early cataracts, thin atrophic retinae with pallor of optic discs, multiple small renal cortical cysts, and runs of high amplitude sharp activity over the vertex on electroencephalogram. Results of urine and plasma bile acids analysis were consistent with a disorder or peroxisome biogenesis. The infant expired soon after return from abroad at the age of 4 months.

**Discussion**

Infants with Zellweger syndrome have a striking constellation of clinical features. The typical facial features include a high forehead, shallow supraorbital ridges, upslanting palpebral fissures, flat and broad nasal bridge, and micrognathia. The facies and occiput are flat. The anterior fontanelle is large. Eye abnormalities include brushefield spots, epicanthal folds, glaucoma, cataracts (80%), pigmentary retinopathy (71%), and optic nerve dysplasia. The neck has redundant folds of skin. Hepatomegaly is usually present. Severe hypotonia (99%) and a weak suck are characteristic. Neonatal seizures are common (80%). Most infants are born by breech presentation. Gallstones, clubfeet, and bilateral knee or hip dislocation were reported in one study from Saudi Arabia.

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Result (μmol/l)</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty acid 22:0</td>
<td>17.5</td>
<td>21.1-102.8</td>
</tr>
<tr>
<td>Fatty acid 24:0</td>
<td>34.5</td>
<td>22.2-86.5</td>
</tr>
<tr>
<td>Fatty acid 26:0</td>
<td>10.46</td>
<td>0.05-1.97</td>
</tr>
<tr>
<td>C24:0/C22:0 Ratio</td>
<td>1.97</td>
<td>0.1-1.15</td>
</tr>
<tr>
<td>C26:0/C22:0 Ratio</td>
<td>0.598</td>
<td>0.0-0.028</td>
</tr>
<tr>
<td>Phytanate</td>
<td>5.20</td>
<td>0-10</td>
</tr>
<tr>
<td>Pristanate</td>
<td>0.94</td>
<td>0-1.00</td>
</tr>
</tbody>
</table>

Figure 2: Knee joint X-ray showing stippled calcification of patella

Severe feeding difficulties and a marked failure to gain weight complicates the post-natal course. Prolonged jaundice and diarrhea are common. Liver function abnormalities may lead to liver failure or cirrhosis. Hepatic and renal cortical cysts (93±9) and proteinuria are often present. Severe psychomotor retardation and seizures are the result of abnormal fetal brain development. Most affected infants die in the first year of life, frequently in the first few months after birth, with average age at death of about 5 months.2,5

The characteristic clinical features in neonatal period of facial dysmorphism, hypertonia, and convulsions in our case prompted us to look for inherited metabolic conditions such as peroxisomal disorders. The stippling calcification of patellae was an additional evidence and the diagnosis was confirmed by the assay of plasma very long chain fatty acids which showed a raised C24:0, and C26:0, and raised ratios of C20:0/22:0 and C26:0/22:0 with a normal phytanic acid level. These results are consistent with a diagnosis of Zellweger syndrome, which is generally considered as the prototype of peroxisomal disorders.2,5

Zellweger syndrome was first described in 1964 by Bowen et al.1 who described a similarly pattern of multiple malformations apparent at birth in two unrelated pairs of siblings. Passarge and McAdams3 reported five similarly affected sisters and introduced the name cerebro-hepato-renal syndrome. The term Zellweger syndrome was propounded by Opitz in 1969 to stress the seminal role played by Hans Zellweger in the identification of the cases initially described by Bowen et al. Goldfischer et al. (1973) reported that patients with Zellweger syndrome lacked demonstrable peroxisomes in their cells.2,5

Peroxisomes are intracellular organelles, measuring 0.5μ and are present in all cells of the body except mature erythrocytes. They are most abundant in liver, kidneys, and adipose tissues. More than forty enzymes are contained within the peroxisomes and they are involved in various catabolic and anabolic functions of the cells such as β-oxidation of very long chain fatty acids (VLCFAs), L-pipepolic acid oxidation, bile acid biosynthesis, and etherlipid (plasmalogens) biosynthesis.2,3 Abnormal fatty acids accumulate in peroxisomal disorders and are incorporated into cell membranes resulting in a perturbation of these membranes' microenvironment and the dysfunction, atrophy, and death of vulnerable cells. Peroxinsomal disorders may result from defects in its biogenesis with impairment or loss of multiple peroxisomal functions, or defects in a single enzyme or pathway.1,2 Twenty-five peroxinsomal disorders have been identified at this time.5 At least 13 different PEX-genes are involved in peroxinsomal disorders, out of which seven have been identified.1 Defects in PEX1, 2, 5, 6, 10 and 12 are associated with the Zellweger phenotype, which is an example of defective peroxinsomal biogenesis. Wands has recently proposed a classification based on clinical grounds.11

The classic clinical picture usually suggests the diagnosis. Stippled calcification of patellae and epiphysis occur in about 69% of cases. Colpocephaly, hypodensity of white matter, and absence of corpus callosum may be seen on CT scan of brain.10,13,19 Electroencephalograph in the inter-ictal phase shows bilateral independent multifocal spikes, predominantly in the frontal motor cortex and surrounding region. Serum iron and copper levels are elevated.

Demonstration of elevated plasma levels of very-long-chain fatty acids especially fatty acid C26:0 and a raised 26:0/24:0 ratio supports the diagnosis and is a highly reliable test for peroxinsomal biogenesis or peroxinsomal β-oxidation.1,12,16 This should be followed up by plasma and urine bile acids, skin fibroblast culture, and morphology of hepatic peroxinsomes.1 Zellweger syndrome is inherited in an autosomal recessive fashion. Prenatal diagnosis by chorionic villous sampling (CVS) or amniocentesis is possible.2,5 Carrier detection is not possible at present time.

Because of the multiplicity and severity of defects, only supportive and symptomatic care is recommended for patients with classic Zellweger syndrome. For patients with milder variants, considerable success has been achieved with multidisciplinary early intervention, including physical and occupational therapy, hearing aids, alternative communication, nutrition and support for the parents. Although most patients continue to function in the profoundly or severely retarded range, some make significant gains in self-help skills, and several are in stable condition in their teens or even early twenties. Specific experimental therapies include the oral administration of plasmalogens in the form of butyl alcohol 5-10 mg/kg/24 hr in 5-8 divided doses and decreased phytanic acid intake. It is not known whether these nutritional measures are of benefit.12

References


