Case Reports

Zellweger's Syndrome

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Zellweger's (cerebrohepatorenal) syndrome is a rare peroxisomal disorder characterized by mongoloid facies, psychomotor retardation, seizures, hepatomegaly, renal cysts and cardiac malformations(l). It result from a failure of peroxisomol biogenesis with multiple enzyme defects and an accumulation of very long chain fatty acids (VLCFA)(2). Zellweger's syndrome which is **a** rare but important cause of neonatal seizures(3), can be diagnosed by characteristic clinical appearance and the measurement of VLCFA levels so that counselling and antenatal diagnosis can be offered for the next pregnancy. We report three cases of Zellweger's syndrome, two of whom were diagnosed in the newborn period.

Case Reports

Case 1: A term breech delivery, born of a third degree consanguineous marriage to Muslim parents, presented on day three of life with refusal of feeds, lethargy, multifocal convulsions resistant to therapy and irregular jerky respiration. The antenatal period and delivery were uneventful and the child cried immediately after birth. On examination, the child had dysmorphic facies, with a wide open anterior fontanelle, high forehead, flattened occiput and a low and broad nasal bridge *(Fig. 1).* There was bilateral proptosis with cloudy corneae, epicanthal folds and optic disc pallor. Bilateral simian creases and talipes equinovarus deformity were present. The child was lethargic with a poor cry and reduced spontaneous activity. There was global hypotonia, areflexia and absent Moro's and suck reflexes. A loud pansystolic murmur of a ventricular septal defect was heard. The liver was enlarged 5 cm below the costal margin, and was of firm consistency. Kidneys were not ballotable. The patient expired on day eight of life. Investigations revealed normal blood counts and platelet count. There was persistent metabolic acidosis and hypoglycemia. Liver function tests and renal function tests were normal. Cerebrospinal fluid examination showed no evidence of infection. Sonography of the skull was normal. Abdominal sonography revealed hepatomegaly with normal liver architecture. CT scan and MRI were not possible in view of the poor general condition of the patient. EEG was normal for age. 2D-ECHO showed a large perimembranous VSD with a bidirectional shunt. Karyotype was normal. VLCFA showed a markedly increased ratio of the very long chain fatty acids (details given in *Table I).* Post mortem brain showed altered cytoarchitecture and abnormal myelini-

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zation. Liver biopsy revealed altered hepatic architecture with cholestasis and dense fibrosis. Iron staining showed increased iron deposition in the liver. Multiple small cysts were seen throughout the renal parenchyma.

Case 2: A neonate presented on day 3 of life in an identical manner with profound hypotonia, intractable seizures, hypoglycemia and failure to thrive. The child had mongoloid facies, hepatomegaly, bilateral enlarged kidneys and a large ventricular septal defect. The child died within the neonatal period from cardiorespiratory failure. VLCFA was characteristically elevated. The details of clinical and laboratory findings are described in *Table I.*

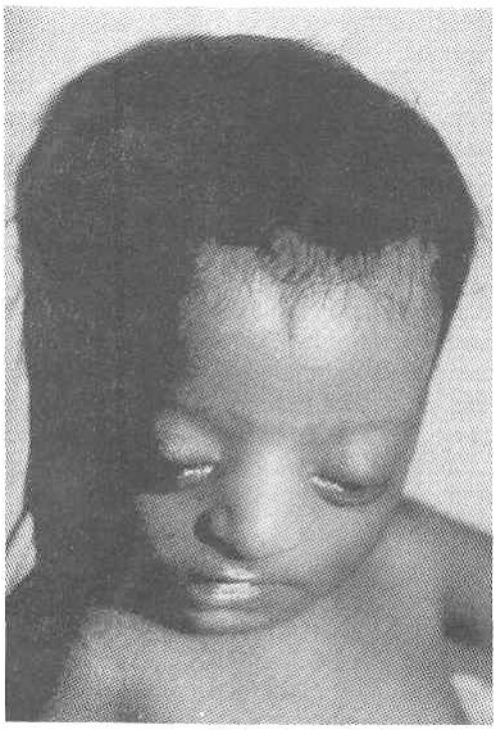

Fig. 1. Note the prominent forehead, hypertelorism, epicanthal folds, hypoplastic supraorbital ridge and depressed nasal bridge in a newborn with Zellweger's syndrome (case 1).

Case 3: A $2^{1/2}$-month-old infant presented with failure to thrive, hepato megaly, hypotonia and mongoloid facies. X-ray of the lower limbs showed patellar calcification *(Fig. 2)* and other investigations *(Table I)* confirmed the diagnosis of Zellweger's syndrome. The child expired at four months age.

Discussion

Peroxisomal disorders include a group of genetically determined conditions in

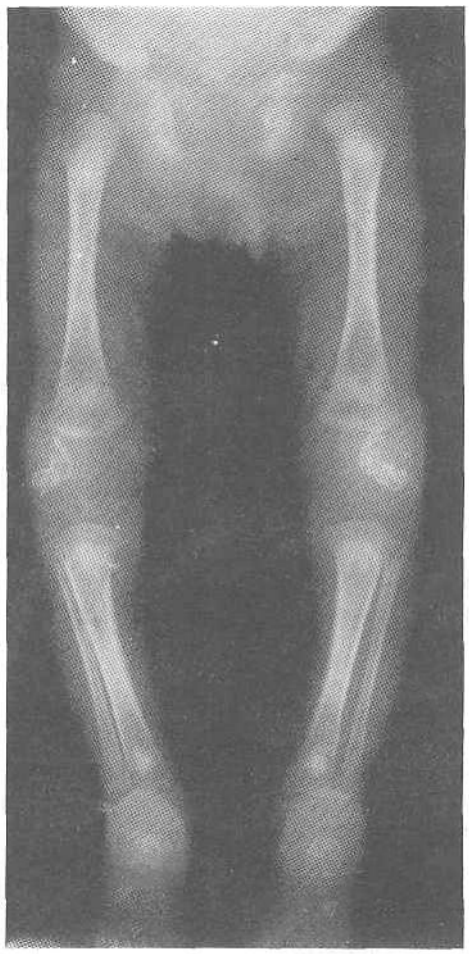

Fig. 2. Abnormal calcific stippling of the patella in an infant with Zellweger's syndrome (case 3).

TABLE I–*Summary of Investigations.*

Investigations	Normal values	Case 1	Case 2	Case 3
1. VLCFA*				
C26/C22	0.01	0.578	0.426	0.734
C24/C22	0.84	2.046	3.510	2.401
C26/C24	0.33	2.465	1.998	3.598
2. Plasma pipecolic acid (mmol/L)	2.1	33.1	18.6	37.1
3. Phytanic acid (μg/ml)	3-7	3	4.6	0.092
4. Karyotype	–	Normal	Normal	Normal
5. EEG	–	Suggestive of Cytoarchitectural abnormality	Same as case 1+ generalized seizure disroder	Not done
6. Biochemical tests	–	Elevated liver enzymes and hyperbilirubinemia	Normal	Direct hyperbilirubinemia
7. 2D-ECHO	–	Large perimembranous VSD	Same as case 1	Normal
8. Post mortem biopsy				
Brain		Edema, demyelination, gross disruption of cellular architecture in the cortex	Cytoarchitectural derangement with pachygyria	Not performed
Liver		Cholestasis and dense fibrosis. Increased iron deposition	Fibrosis	Not performed
Kidneys		Glomerular microcysts	Large cortical cysts of glomeular and tubular origin	Not performed

* VLCFA levels were done at Peroxisomal Disease Laboratory, Kennedy Krieger Institute, Baltimore, USA.

which the major pathology is a defective form or number of peroxisomes or a defective function of one or more enzymes located within this organelle(4). Zellweger's syndrome occurs with a frequency of 1:100,000 live births(5). It is inherited as an autosomal recessive condition. Cytogenetic studies show a microdeletion or pericentric inversion on chromosome 7:7q11.23 is the most likely location(6). We did not find any karyotypic abnormalities in our cases. The cause of Zellweger's syndrome is a failure to import the newly synthesized peroxisomol proteins into the peroxisomes. The proteins remain in the cytosol where they are rapidly degraded and the peroxisomol membranes persist as empty "ghosts" of the organelle. Malfunctioning

of the enzyme import mechanism may be the key abnormality(5).

Accumulation of very long chain fatty acids results in multiple organ involvement. Cytoarchitectural abnormalities in the brain result from disordered neuronal migration. The cerebral convolutions are abnormally small (-microgyria) or thick (-pachygyria)(7). In a majority of patients the liver is enlarged and fibrotic, as was noted in all these 3 cases(7). Eventually micronodular cirrhosis and excessive iron deposits are found. Renal cysts, varying in size from glomerular microcysts to large cortical cysts of glomerular and tubular origin are seen in 80% of patients(7). Calcific stippling of the patella with synchondrosis of the acetabutum occurs in upto 50% of patients, as was seen in *Case 3*. Premature patellar calcification and renal changes may be seen as early as the second trimester(8).

In our patients the presence of hypotonia and "mongoloid fades" made us initially suspect Down's syndrome. However, the presence of profound hypotonia, neonatal seizures, hepatomegaly, enlarged kidneys and eye changes led us to consider Zellweger's syndrome as a possible alternative diagnosis. 'Down's like' facies are also seen in Rhizomelic chondrodysplasia punctata, but the absence of rhizomelic limb shortening, ichthyosiform skin changes of the pathognomic appearance of stippled calcification in the hyaline cartilage ruled out this disorder(5).

The diagnostically significant abnormality is a defective oxidation and accumulation of VLCFA. Plasma hexacosanoic acid (C26) levels are increased nine fold or more over control levels. Also, docosanoic acid (C22) levels are decreased resulting in a strikingly abnormal C26: C22 ratio of 0.49 + 0.03 in Zellweger's syndrome (normal= 0.014). Similarly the ratio of other VLCFA, *e.g.*, C24/C22 is also markedly increased. Abnormalities in phytanic acid and plasmalogens are age dependent and may not be demonstrable before 20 weeks postnatal age(9). Reduction in the number of peroxisomes may be appreciated on electron microscopy.

Prenatal diagnosis may be performed by demonstrating increased levels of VLCFA in cultured amniocytes and chorion villus biopsy samples(6). There are no techniques available for heterozygote identification. Current experimental protocols using clofibrate, glycerol and the oral administration of docosahexanoic acid(10) are being tried in an attempt to achieve postnatal correction of the biochemical abnormalities. However, in view of the multiplicity and severity of the defects only supportive care is recommended. Most patients succumb by 6 months of age, as was seen in all 3 cases. Antenatal diagnosis and therapeutic abortion remain the only available options.

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