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Case Report

Prenatal and post-natal imaging of Zellweger spectrum disorder with novel prenatal sonographic findings

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ABSTRACT

Peroxisomes are membrane-enclosed organelles in the cell which contain enzymes involved in various metabolic processes. Peroxisomal disorders are classified as peroxisome biogenesis disorder and single enzymatic defects. Zellweger spectrum disorder is an autosomal recessive condition affecting any of the 13 PEX genes responsible for synthesis and functioning of the peroxisomes. Prenatal diagnosis of Zellweger spectrum disorder has been possible in the recent years due to clinical exome sequencing of the amniotic fluid or chorionic villous sampling in suspected cases. The common prenatal imaging findings are Fetal akinesia/bradykinesia, Ventriculomegaly and echogenic kidneys. We present a case of antenatally suspected Zellweger syndrome, its post-natal imaging with confirmation of diagnosis by biochemical studies and clinical course. A 36-year-old multigravida, known case of SLE, was referred to us for a detailed anomaly scan at 25 weeks of gestation in view of fetal ventriculomegaly. Additional prenatal imaging findings were fetal hypokinesia, rhizomelia, persistent left SVC, echogenic kidneys, hepatomegaly with calcification, polyhydramnios and intrauterine growth restriction. Postnatally, neonate had dysmorphic facial features of high forehead, shallow supraorbital ridges, low-set ears with absent antihelix, hypertelorism, depressed nasal bridge, upturned nasal tip, and absent eyelashes. The neonate had repetitive seizures and elevated transaminases. On abdominal ultrasound, hepatomegaly with hepatic calcification, bilateral echogenic kidneys with cysts within were noted. On neurosonogram, lateral ventriculomegaly with bilateral germinolytic cysts was noted. An infantogram showed irregular stippled calcification of the epiphyses of bilateral patella, calcaneum, femoral head and olecranon. MRI brain showed bilateral lateral ventriculomegaly, brachycephaly with bilateral frontal and peri-sylvian polymicrogyria. The plasma of the neonate showed elevated very long-chain fatty acids and low plasmalogens. These biochemical findings are suggestive of peroxisome biogenesis disorder/RCDP. Our case reconfirms the most common prenatal findings of Zellweger spectrum disorder. The novel prenatal finding in our case was the hypoechoic enlarged liver with parenchymal calcification, IUGR, late onset polyhydramnios, and persistent left SVC. The overall prognosis of this disease is dismal, hence early prenatal detection is of utmost importance.

Keywords: Zellweger syndrome, Ventriculomegaly, Fetal hypokinesia, Echogenic kidneys, Rhizomelia

INTRODUCTION

Peroxisomes are membrane-enclosed organelles in the cell that contain enzymes involved in various metabolic processes. They include nearly 50 enzymes that help in the catabolism of uric acid, amino acids, long-chain fatty acids, and reactive oxygen species. Peroxisomes are also involved in the biosynthesis of cholesterol, bile acids, and plasmalogens. Plasmalogens form an integral part of the cell membrane in the heart and brain.[1]

Peroxisomal disorders are classified into 2 types-peroxisomal biogenesis disorder, single enzymatic defect.

Zellweger spectrum disorder is an autosomal recessive condition affecting any of the 13 PEX genes responsible for the synthesis and functioning of the peroxisomes.[2] The neonates born with this disorder have typical facial appearance, generalized hypotonia, refractory seizures, and eye abnormalities. More than 90% show post-natal growth failure and rarely live more than a few months.[3] Prenatal diagnosis of Zellweger spectrum disorder has been possible in recent years due to clinical exome sequencing of the amniotic fluid or chorionic villous sampling in suspected cases.[4] The common prenatal imaging findings are Fetal akinesia/bradykinesia, Ventriculomegaly, and echogenic kidneys. We present a case of antenatally suspected Zellweger syndrome, its post-natal imaging with confirmation of diagnosis by biochemical studies and clinical course. To our knowledge, our case is probably the second one with overlapping features of Zellweger spectrum disorder and rhizomelic chondrodysplasia punctata (RCDP). Having a post-natal follow-up makes our case unique.

CASE REPORT

A 36-year-old G5P2A2L2, a known case of SLE with lupus nephritis stage IV, was referred to us for a detailed anomaly scan at 25 weeks of gestation because of fetal ventriculomegaly. She was on steroids and mycophenolate mofetil and attained remission at 26 years of age and later switched to hydroxychloroquine (HCQ). Due to HCQ toxicity, her medications were changed to losartan (stopped in 2nd month of gestation) and aspirin. At 25 weeks of gestation, the fetus showed ventriculomegaly, hypokinesia with rhizomelia (femoral length <1 centile), and polyhydramnios (Figure 1 A-C). On fetal echocardiography, there was Persistent left SVC (Figure 1 D and E). Thereafter, the patient was followed up every four weeks till term to look for developing aortic arch anomalies. Maternal IgM TORCH titres were negative. At 32 weeks of gestation, the fetus had persistent hypokinesia, bilateral normal-sized echogenic kidneys, and a hypoechoic enlarged liver with a large hepatic calcification (Figure 1 G and H). There was growth restriction (fetal weight less than 3rd centile) with normal Doppler parameters. There was polyhydramnios with a progressive increase in ventriculomegaly (Figure 1 F). No aortic arch abnormality was noted. Given the above findings, a suspicion of metabolic disorders like Zellweger syndrome was raised. However, patient refused prenatal fetal MRI/amniocentesis. At 39 weeks of gestation, a female neonate was delivered by an emergency caesarean section. The neonate did not cry immediately after birth and required resuscitation in form of intermittent positive pressure ventilation for 30 seconds with APGAR scores at 1 and 5 minutes being 7/10 and 8/10 respectively. She was shifted to intensive care unit and on clinical examination at birth, the child was lethargic and hypotonic. There were dysmorphic facial features including a high forehead, shallow supraorbital ridges, low-set ears with absent antihelix, hypertelorism, depressed nasal bridge, upturned nasal tip, and absent eyelashes (Figure 2).

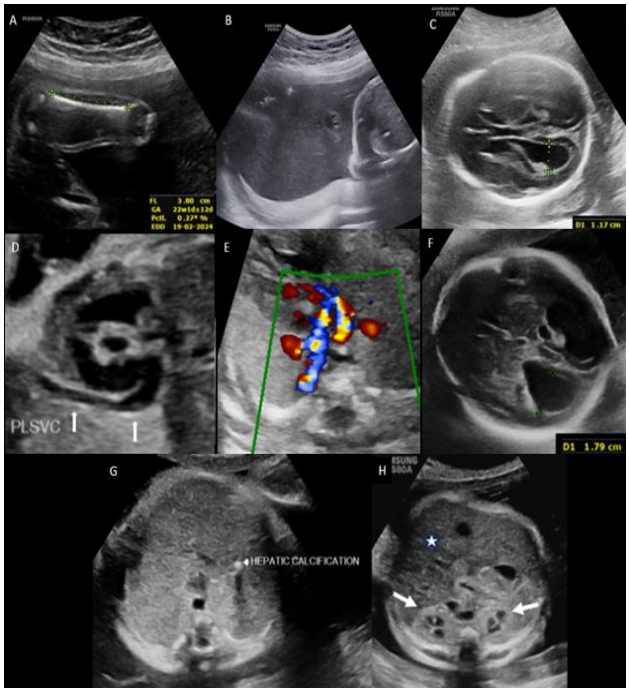

Figure 1: B-mode ultrasound of the fetus shows short femur length less than 1st centile (A) with polyhydramnios (B) and mild ventriculomegaly (C) at 25 weeks of gestation. B-mode and colour Doppler image showing persistent left SVC draining in the coronary sinus (D) and in the three-vessel view (E). B-mode axial trans-ventricular section of fetal brain at 32 weeks shows severe ventriculomegaly measuring 17.9 mm (F). Axial section of the fetal abdomen shows a single focus of hepatic calcification (G) and (H) shows bilateral echogenic kidneys (solid arrows). The liver in image (H) appears hypoechoic (star).

Figure 2: Dysmorphic facial features include low-set ears, hypertelorism, upturned nasal tip, absent eyelashes, shallow supra-orbital ridge, and depressed nasal bridge.

Head examination revealed macrocephaly with a head circumference of 34 cm. The child had rhizomelic shortening of lower limbs. (Table 1) The Moro's reflex and suck reflex were poor. Bilateral corneal haziness was present on ophthalmologic evaluation. The neonate also developed repeated episodes of unifocal seizures since day 1 of life. The blood investigations done have been summarised in Table 2. On post-natal ultrasound, the Liver was hypoechoic, and enlarged, with increased periportal echogenicity. Prenatally noted hepatic calcification was seen. Both the kidneys were echogenic with multiple small variable-sized simple cortical cysts (Figure 3). On the neurosonogram, there was lateral ventriculomegaly with bilateral germinolytic cysts and thinned-out corpus callosum (Figure 4). The patellar epiphyses ultrasound showed dense premature calcification. (Figure 5 A). Echocardiography of the neonate revealed persistent left SVC with ostium secundum ASD. An infantogram for evaluation of rhizomelic shortening showed irregular stippled calcification of the epiphyses of the bilateral patella, calcaneum, femoral head, and olecranon. (Figure 5 B). MRI brain of the neonate revealed age-appropriate myelination. There was bilateral lateral ventriculomegaly predominantly involving occipitotemporal horns, and brachycephaly (Figure 6 A and B) with bilateral frontal and peri-sylvian polymicrogyria (Figure 6 C-E) suggestive of neuronal migration disorder.

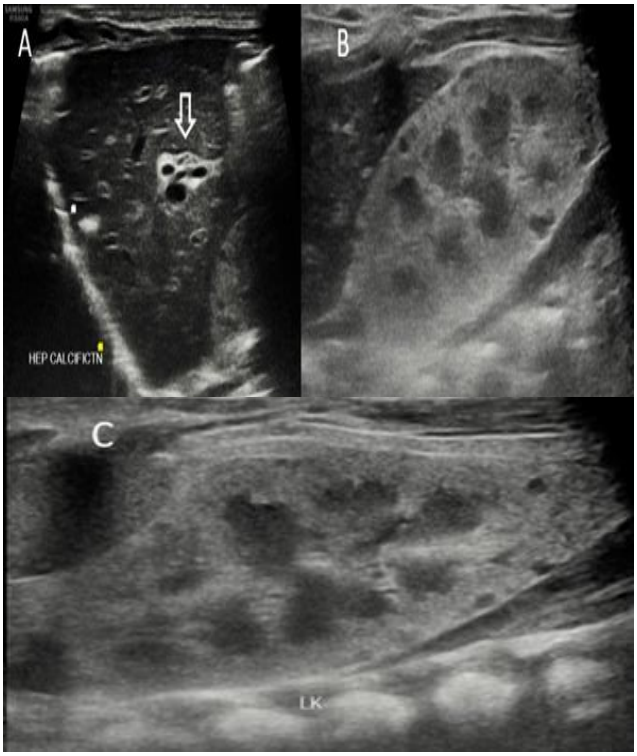

Figure 3: B-mode axial section of the neonatal abdomen shows (A) hypoechoic liver parenchyma with increased periportal echogenicity (open arrow) with a small hepatic calcification in the right lobe. (B and C) Longitudinal sections of both kidneys show increased cortical echogenicity with multiple small cortical cysts.

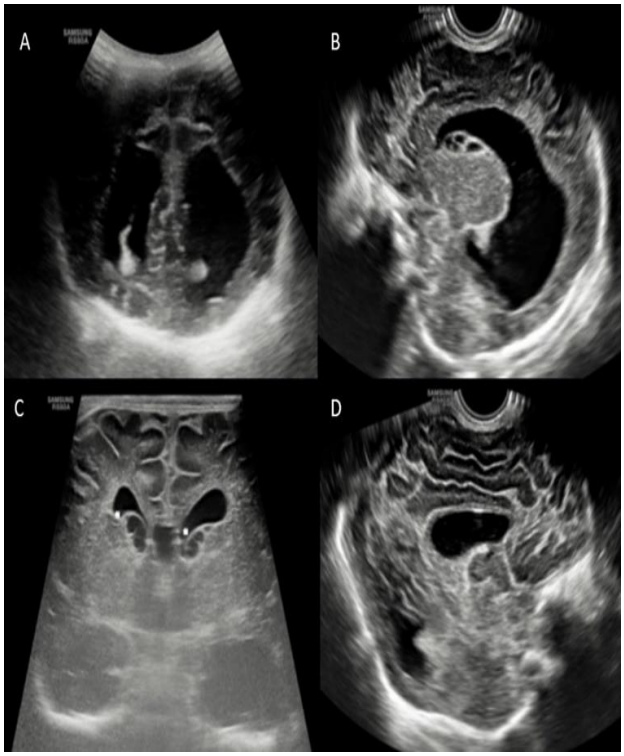

Figure 4: Transcranial B-mode ultrasound of neonatal brain in coronal section (A) and parasagittal section (B) shows dilated lateral ventricle. (C) Subependymal germinolytic cysts (solid arrows) are noted bilaterally. (D) Sagittal section shows thinned-out corpus callosum.

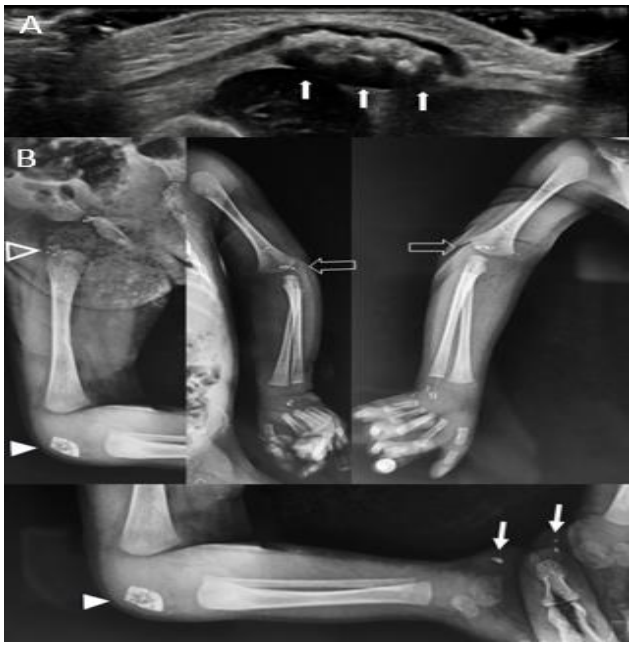

Figure 5: B-mode ultrasound of the long axis of the patella (A) shows irregular calcification of the epiphyses confirmed on infantogram (B) shows stippled and irregular calcification of the epiphyses of calcaneum (arrow), patella(arrowhead), olecranon (open arrow), and femoral head (open arrowhead).

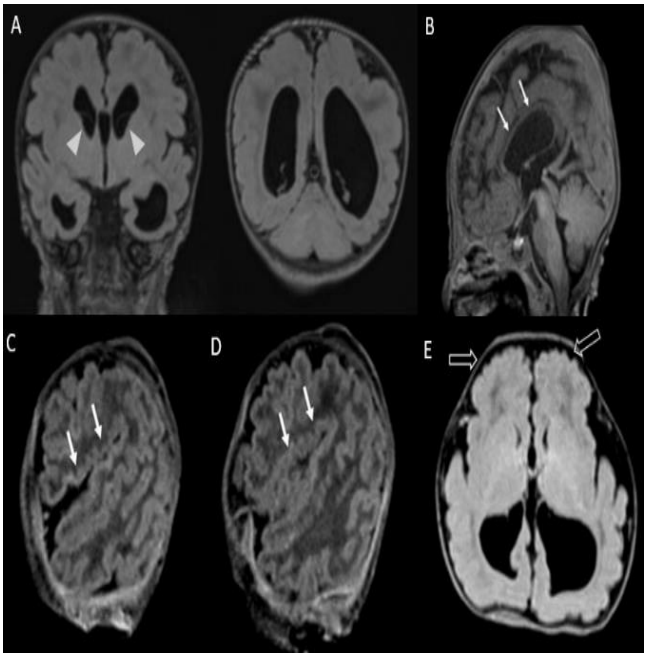

Figure 6: (A) STIR coronal and sagittal T1 weighted images of neonatal brain show dilatation of lateral ventricles with bilateral subependymal germinolytic cysts (arrowheads) and thinned-out corpus callosum in (B) (solid arrows). There is also brachycephaly. T1 weighted parasagittal section of right and left insular region (C and D) shows abnormally thickened cortex with jagged gray-white matter junction to suggest polymicrogyria respectively (solid arrows). (E) STIR axial sections show bilateral frontal polymicrogyria (open arrow).

The clinical differentials in view of chondrodysplasia punctata in a dysmorphic baby born to a mother with lupus were Zellweger syndrome and neonatal lupus. Plasma of the neonate was sent for quantification of very long-chain fatty acids and serum plasmalogens. The C26:0 fatty acids and the C26/C22 ratios were significantly elevated (Table 3). Plasmalogen to fatty acid ratios were low (Table 3). These biochemical findings are suggestive of peroxisome biogenesis disorder/RCDP. Multidisciplinary treatment was initiated for neonate involving oxygen support and antiepileptics. However, child succumbed at 1 month of age due to refractory seizures and respiratory failure.

Table 1: Anthropometry details of the neonate

Variables	Birth	50th %	Centile
Weight	2260 gm	3300 gm	<3rd centile
Length	43 cm	49.5 cm	<3rd centile
Head circumference	34 cm	34 cm	At 50th centile
Variables	**Right (in cm)**	**Left (in cm)**	**Inter-pretation**
Arm	8	8	Below -2 SD
Forearm	8	8	At mean
Hand	6	6	Between mean and -2 SD
Thigh	17.5	17.5	Below -2 SD
Leg	17	17	Between mean and -2 SD
Foot	7.5	7.5	Between mean and -2 SD

Table 2: Investigations of the neonate.

Lab investigation	Patient value	Normal reference range	Interpretation
Complete blood count			
Haemoglobin (gm %)	21	13.4 to 23.7	Normal
PCV (%)	60.5	45 to 65	Normal
Total leukocyte count (cells/mm^3)	11400	5000 to 25000	Normal
Platelet (lakhs/mm^3)	4	1.5 to 4.7	Normal
Blood sugar (mg/dl)	95	60-125	Normal
Blood gas (venous)			
pH	7.31	7.35 to 7.45	Normal ABG
pCO2 (mm Hg)	41	35 to 45	
pO2 (mm Hg)	43	50 to 70	
Bicarbonate (mEq/l)	20.6	18 to 24	
Liver markers			
SGOT (U/l)	175	9 to 80	Elevated
SGPT (U/l)	99	13 to 45	Elevated
Total proteins (gm %)	5.4	5-7.5	Normal
Serum albumin (gm %)	3.6	3-5	Normal
Serum calcium (mg%)	8	9 to 11	Hypocalcemia
Serum phosphorus (mg%)	4.8	4 to 6.5	Normal
Alkaline phosphatase (U/l)	91	50 to 370	Normal
ANA blot	Positive for anti-histone antibodies		Due to passage of antibodies from mother's milk
Ophthalmic evaluation	Bilateral corneal haziness		

Table 3: Plasma very-long chain fatty acids and plasmalogens values of the neonate.

Variables	Result	Normal range	Interpretation
Plasmalogen/fatty acids ratios			
C16:0 DMA/C16:0 fatty acid	0.0321	0.051-0.090	Low plasmalogens/fatty acid ratios, suggestive of peroxisome biogenesis disorders.
C18:0 DMA/ C18:0 fatty acid	0.0451	0.137-0.225	
Plasma total lipid-very long chain and branched chain fatty acids			
Pristanic acid	0.13	<0.45 ug/ml	Normal
Phytanic acid	1.56	<3.00 ug/ml	Normal
C22:0	9.79	20.97±6.27	Low (Zellweger: 8.66±4.97)
C24:0	18.49	17.59±5.36	Normal
C 26:0	1.70	0.23±0.09	Elevated (Zellweger: 1.0±1.50)
C24/C22	1.90	0.84±0.10	Elevated (Zellweger: 2.07±0.28)
C26/C22	0.17	0.01±0.004	Elevated (Zellweger: 0.50±0.16)

DISCUSSION

Zellweger syndrome was first described by Bowen et al as familiar disorder of multiple congenital defects.[8] It is predominantly characterised by renal, skeletal, hepatic, craniofacial and neurological abnormalities. Renal abnormalities include renal cortical microcysts.[9] Skeletal manifestations include rhizomelic chondrodysplasia punctata.[10] Hepatic manifestations include hepato-splenomegaly and liver cirrhosis.[9,11] Craniofacial abnormalities include a large anterior fontanel with widely spaced sutures, broad, full forehead, micrognathia external ear deformity, low and broad nasal bridge, shallow orbital ridges, and redundant skin folds in the neck. Clinically, the neonates have low APGAR score at birth with profound hypotonia, areflexia and repeated episodes of seizures.[12] The neurological manifestations of the disease spectrum consist of three histopathological features i.e., neuronal migration abnormalities, white matter abnormalities and selective neuronal involvement. Radiologically, these manifests as ventriculomegaly, peri-ventricular leukodystrophy, perisylvian and frontal pachygyria-polymicrogyria and germinolytic cysts.[9] Most of these features can be detected on prenatal ultrasound and MRI. The key prenatal imaging findings in our case were fetal bradykinesia with rhizomelia, progressive ventriculomegaly, renal hyperechogenicity, hypoechoic hepatomegaly with calcification, IUGR, late onset poly hydramnios and persistent left SVC. Fetal bradykinesia and increased nuchal translucency had been previously described as a first trimester ultrasound marker of Zellweger syndrome by Johnson.[6] Ventriculomegaly, renal hyper echogenicity, growth restriction, hepatomegaly with heterogenous hypo-intensity of liver parenchyma on MRI has been previously described in a case report by Mochel et al.[11] We came across prenatal hypoechoic liver parenchyma with a hepatic calcification in our case. Rhizomelic chondrodysplasia punctata is well-established prenatal imaging finding reported by Ashwini et al in retrospective study of 62 fetuses.[10] This finding was established postnatally in our case. Previously undescribed and novel findings in our case late onset polyhydramnios and persistent left SVC. We believe that cause for poly-hydrammios in second and 3rd trimester is decreased fetal swallowing due to global hypotonia. We could not find any association between persistent left SVC and Zellweger syndrome.

Prenatal fetal MRI provides additional imaging findings of pachygyria polymicrogyria, periventricular leukodystrophy and germinolytic cysts in the fetal brain and renal cortical cysts[7] which may not be visualised optimally on prenatal ultrasound.[9] Findings of polymicrogyria and renal cortical cysts were found postnatally in our case.

A confirmatory prenatal diagnosis is done by biochemical evaluation of peroxisomal enzyme activity or whole exome sequencing of the PEX genes from the chorionic villous sampling or amniotic fluid. In our case, the patient denied any invasive procedure. The diagnosis was achieved by the presence of elevated levels of very long chain fatty acids and low levels of plasmalogens in the plasma of the neonate.

CONCLUSION

Our case reconfirms the most common prenatal findings of Zellweger spectrum disorder which are fetal bradykinesia, IUGR, renal hyperechogenicity, and progressive ventriculomegaly with or without rhizomelia. The novel prenatal finding in our case was the hypoechoic enlarged liver with parenchymal calcification, late-onset polyhydramnios, and persistent left SVC. Prenatal diagnosis of this disorder is possible by biochemical evaluation of peroxisomal enzyme activity or whole exome sequencing of the PEX genes from the chorionic villous sampling or amniocentesis. Prenatal MRI plays a crucial role in the early detection of cortical malformations associated with this condition. Post-natal neuroimaging and abdominal imaging with biochemical studies aid in the confirmatory diagnosis of this disease as in our case. The overall prognosis of this disease is dismal, hence early prenatal detection is of utmost importance.

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