Case Report

Zellweger Syndrome: A Downs Syndrome Mimic

Khadpe T.[1], Kondekar A.[2], Anand V.[3], Ghildiyal R.[4]

[1]Dr. Tanmay Khadpe, Post Graduate Resident, [2]Dr. Alpana Kondekar, Associate Professor, [3]Dr. Varun Anand, Assistant Professor, [4]Dr. Radha Ghildiyal, Professor, Department of Pediatrics, All authors are affiliated with TN Medical College and BYL Nair Hospital, Mumbai Central, Mumbai, India.

Corresponding Author: Dr. Tanmay Khadpe, Post Graduate Resident, Department of Pediatrics, TN Medical College and BYL Nair Hospital, Mumbai Central, Mumbai, India. E-mail: tanmay.khadpe@gmail.com

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Abstract

The peroxisomal diseases are genetically determined disorders caused either by the failure to form or maintain the peroxisome or by a defect in the function of a single protein that is normally located in this organelle. It is a heterogeneous group of autosomal recessive disorders characterized by a defect in peroxisome formation and are caused by mutations in one of 13 PEX genes. The defect in peroxisome formation or impaired metabolic pathways result in metabolic abnormalities. Typically in Zellweger spectrum disorders (ZSD) patients accumulate very long chain fatty acids (VLCFAs), phytanic and pristanic acid, C27-bile acid intermediates and pipecolic acid in plasma and have a deficiency of plasmalogens in erythrocytes.These disorders present with a wider range of phenotype than has been recognized in the past and few of them may phenotypically resemble Downs Syndrome.

Keyword: Peroxisomal diseases, PEX genes, Zellweger spectrum disorders, Very long chain fatty acids, Plasmalogens, Downs Syndrome

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Introduction

Zellweger syndrome (ZS) as a cerebro-hepato-renal syndrome was first described in 1964 by Bowen et al [1]. The clinical presentations have clinical overlap in terms of morphological features. Some of the phenotype mimic Downs syndrome [1,2]. Despite of being a cerebro-hepato-renal syndrome in literature, we present a case with predominant neurological involvement without any hepatic or renal manifestations at presentation. The diagnosis was suspected only on basis of clinical phenotype resembling downs syndrome with a normal karyotype.

Case Summary

We report a case of 3-month-old girl presented with fever and vomiting for 3 days with lethargy, refusal to feeds for a day prior admission. There was no significant past history and family history. Perinatal period was uneventful however antenatal ultrasound was suggestive of polyhydramnios.The child presented in status epilepticus, jerky respiration and apneic spells.

On general examination, patient was afebrile, lethargic, with feeble pulses and delayed capillary refill time.Head circumference was 42 cm (Normocephaly). However our patient had marked frontal bossing, dolichocephaly, mongoloid slant, ear lobules bilaterally hypoplastic, depressed broad nasal bridge, lower lid eyelashes sparse, Anterior fontanelle was open (normal size) (Fig1and 2).

The hand of the patient had simian crease with clinodactyly, absent bilateral proximal interphalangeal flexure lines on index finger, middle finger and no flexure lines on bilateral little finger. No neurocutaneous markers were present. Spine was normal (Fig 3 and 4) On Systemic examination child had marked hypotonia, hyper reflexia, firm hepatomegaly. Fundus examination was normal.

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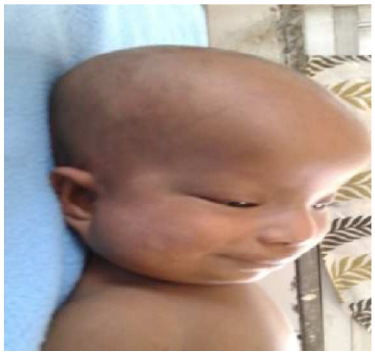


Figure 1 and 2: Lateral view showing frontal bossing, depressed nasal bridge, low set ears, hypoplastic ears, hypoplastic supraorbital ridges. Anterior view showing telecan thus, parietal bossing, mongoloid slant

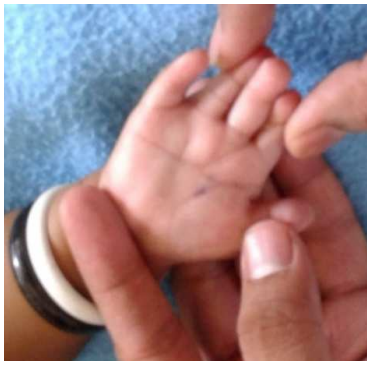
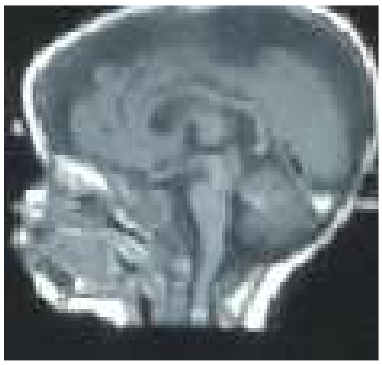


Figure 3 and 4: Palmar view of right hand showing short fingers with simian crease, absent proximal interphalangeal flexure lines on index finger, middle finger and no flexure lines on little finger.

Child required ventilatory support and was stabilised with treatment with antibiotics for 3 days, inotropic support for first 24 hours of admission. Status epilepticus was controlled by Fosphenytoin, Phenobarbitone, Levetiracetam. After initial stabilisation she was further evaluated for dysmorphism mimicking Downs syndrome. Karyotype (46XX) and Thyroid function tests done postnatally were normal.

MRI was suggestive of chronic subdural collections with mild diffuse cortical atrophy in Bilateral Fronto-parieto temporal regions with cystic hygroma in frontal region (Fig 5)



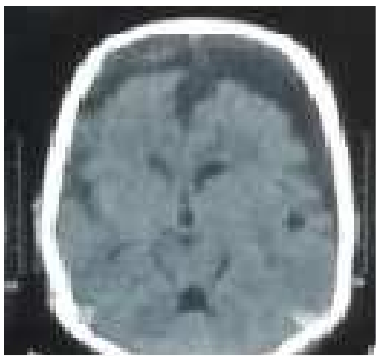


Figure 5: MRI T1 weighted saggital and axial planes suggestive of chronic subdural collections with mild diffuse cortical atrophy in Bilateral Frontoparieto temporal regions with cystic hygroma in frontal region

Child was planned for a work up keeping Zell wegers Spectrum disorders owing to a phenotype suggestive of Downs syndrome but a normal karyotype. Hence a Very long chain fatty acid assay was done which reported an elevated C26 and C26/C22. RBC plasmalogen/Fatty acid ratio reported normal C16:0 DMA/C16:0 fatty acid and low C18:0 DMA/C1:0 fatty acid ratios. The report was hence consistent with Zell wegers Syndrome.

Child was discharged on a phytanic free diet, antiepileptics, docosahexaenoic acid (DHA) and multivitamin supplementation. Child was followed up on monthly intervals however patient did not follow up after 6 months of age. The plan for further confirmation of diagnosis in cultured skin fibroblast**,** DNA sequencing of PEX and related peroxisomal single enzyme defects genes for mutations as mentioned in literature were not feasible due to financial constraints [1].

Discussion

Peroxisome biogenesis disorders, Zellweger syndrome spectrum (PBD, ZSS) is a continuum comprising three phenotypes-

1. Zellweger syndrome (ZS), the most severe
2. Neonatal adrenoleukodystrophy (NALD);
3. Infantile Refsum disease (IRD), the least severe

Children with the severe phenotype (neonatal-infantile presentation with severe clinical symptoms) have a poor prognosis and these patients usually die within the first year of life.

Patients that present in childhood or adolescence usually have a better prognosis, but can develop progressive liver disease or leukodystrophy and gradually deteriorate. Despite early presentation with ZS our patient did not have any liver involvement. Progressive liver disease or leukodystrophy are poor prognostic indicators.

The remaining milder individuals can reach adult hood without progression or with long periods of stabilization. When progression occurs, it is mainly related to peripheral neuropathy and pyramidal signs, while cognition remains stable. Most patients with ZS succumb in first year of life. The incidence is variable worldwide with highest in Quebec (1 in 12) and lowest inJapan(1 in 5,00,000)[2].

We reviewed other Downs Mimic Syndromes

a) 49, XXXXY chromosome and other high-order multiple X chromosome disorders
b) Congenital hypothyroidism
c) Mosaic trisomy 21 syndromePartial trisomy 21 (or 21q duplication)
d) Robertsonian Translocation
e) Zellweger spectrum disorders

We could narrow down our differentials by karyotype and a normal thyroid function test. The final diagnosis was established based on Very long chain fatty acid and RBC plasmalogen/Fatty acid ratio done as our patient had a Downs phenotype.

MRI was done to look for CNS migration defects. Very long chain fatty acid and RBC plasmalogen/Fatty acid ratio were consistent with Zell wegers Spectrum disorder.

Like any other syndromes, Zell wegers spectrum disorders too have a variation in phenotypes from case to case, we enlist few features in the Table 1 based on earlier reported case reports [3-6].

The treatment modalities at presentdovetail clofibrate, glycerol and the oral administration of DHA in an attempt to achieve postnatal correction of the biochemical abnormalities [4].

However, in view of the multiplicity and severity of the defects only supportive care is recommended. The supportive care would be supplementing cortisone for adrenal insufficiency, Vitamin K supplementation for Coagulopathy, use of antiepileptic drugs for seizure control, oral citrate treatment for hyperoxaluria, Supplementation of fat soluble vitamins (A,D,E), appropriate visual and hearing aids for respective impairment.

Surgical interventions like cataract removal or gastrostomy may be needed as and when warranted.

Table 1: Clinical Features in ZSD.

Morphological Features	Features present in our case	Systemic involvement	Systemic involvement in our case
Head and neck		Cardiac	
High forehead	+	Ventricular septal defects	-
Large fontanelles*	-	Aortic abnormalities	-
Flat occiput	+	Patent ductus	-
Redundant neck skin	-	arteriosum	
Dolichocephaly	+	Endocrine	
Metopic suture	-	Impaired adrenal function	-
Micrognathia	-	Fibrotic pancreas	-
Eyes, ears, nose,		Islet cell hyperplasia	-
mouth	+	Gastrointestinal	
Epicanthus*	+	Pyloric hypertrophy/stenosis	-
Hypertelorism	-	Hepatic	
Cataract/Corneal		Hepatomegaly*	+
clouding	-	Jaundice	-
Brushfield spots	-	Genitalia	
Optic disc pallor	-	Cryptorchidism	NA
Retinitis pigmentosa	-	Hypospadiasis	NA
Glaucoma	-	Clitoromegaly	-
Abnormal retinal		Musculoskeletal	
pigmentation*	+	Chondrodysplasia punctata*	-
Shallow orbital		Shortened proximal limbs*	+
ridges*		Delayed bone age	+
ocular		Myopathy	-
medulloepithelioma		Neurological	
External ear	+	Encephalopathy*	+
deformity	+	Developmental	+
Low/broad nasal		arrest/delay*	
bridge*	-	Abnormal Moro's reflex*	+
Anteverted nares*	-	Severe hypotonia	+
Micrognathia	-	Hyporeflexia/arefelxia	+
High arched palate		Poor sucking/gavage feeding	+
Limb anaomalies	-	Seizures	+
Varus deformity	-	Nystagmus	-
Club feet	+	Impaired vision*	-
Clinodactyly	-	Impaired hearing*	-
Brachydactyly	+/-	Renal	
Simian crease		Hyperoxaluria	-
		Renal Cysts	-
		Nephrolithiasis	-

*Clinical features noted in .50% of patients with ZS and when present together are clinical criteria highly suggestive of a diagnosis of a peroxisomal disorder. The diet in form of phytanic free diet plays an important role for further reducing metabolic stress. Table 2 illustrates the recommend able and avoidable food items in ZS[7,8, 9].

Table-2: Food items recommended and avoidable in ZS.

No phytanic- Safely recommended foods	High Phytanic- Not recommended foods
Fruits, Cereals and vegetables	Fish
sunflower and safflower oils	All milk products
poultry or pig meats	beef, rabbit meats, sheep and goat products
Breast milk (especially of fish consuming mothers for DHA)	

Most patients succumb in infancy. Antenatal diagnosis is hence needed. There is are port on the successful application of Preim plantation genetic diagnosis (PGD) in a family affected with Zellweger syndrome (ZS) caused by a mutation in PEX26 gene. This was the first successful report of PGD for ZS, with the subsequent delivery of a homozygous normal baby after delivering 4 children with ZS and therapeutic abortion may hence not be needed in future[10].

Conclusion

We emphasize the importance of a clinical suspicion of Zell wegers Spectrum Disorders based on the typical phenotype and appropriate metabolic work up for early diagnosis and timely intervention. Supportive management and dietary modification help in improving the quality of life as well as modifying the disease process.

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