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ARTICLE ON AN OVERVIEW OF CLINICAL FEATURES, PEROXIMAL DISORDERS, PROGNOSIS, GENETIC COUNSELING AND CURRENT TREATMENT METHODOLOGIES OF ZELLWEGER SYNDROME.

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ABSTRACT

Zellweger spectrum disorders are the chief subgroup of peroximal biogenesis disorders resulted due to problems in PEX genes. Peroxsoimal biogenesis disorder are resulted due to mutation in well known 13 PEX genes which are used for coding peroxins. The confirmation of peroxisomal biogenesis disorder was done by enzyme analysis and y very long chain fatty acids present in plasma and fibrioblast and also by study of immunoflourescent microscopy. It is one of the well known clinical and biochemical field that is further divided into three clinical phenotypes. It is mainly associated with babies. The defective peroxisomes cause different metabolic disorders which can be mainly perceived in blood and urine. For zellweger syndrome there are no therapies are discovered yet but care and precautions are available. The patients of zellweger syndrome disease have distinct clinacl and facial features, they have short life expectancy mostly upto 1 year.the uses of DNA testing in peroxisomal biogenesis disorder are carrier testing of relatives, testing of parents or genetic preimplantations, diagnosis in families with presence risk of zellweger syndrome disorder and this also help to improve managmentpatients. Sometimes this disease shows misdiagnosis because its symptoms are highly similar to other diseases, so we should perform proper testing to avoid any misleading to any other diseases

INTRODUCTION

Zellweger syndrome, which is also known as cerebrohepatorenal syndrome, is an infrequent inherent disease and it is caused due to deduction or lack of peroxisomes (functionally active) in the individual cells. It is member of group of diseases called “leukodystrophies”.This disease zellweger syndrome is named after Hans Zellweger (1909-1990). He was a famous Swiss-american specialist in pediatrics, he also worked in ‘University of Lowa’ as a professor of genetics and pediatrics and the research on this disease was carried out in the same university (Eengelen*et al*., 2011). Zellweger syndrome is the very harsh type of the spectrum of forms called Zellweger spectrum. Its symptoms and signs usually show up during the earliest stages of newly born and the most common signs and symptoms of zellweger syndrome are named below;

Hypotonia is a syndrome and it is known as floppy baby syndrome. People suffering of hypotonia have relatively lower ability to stretch their muscles and also have less muscle strength. Lack of satisfied feeding is a condition in which babies suffering of zellweger syndrome do not a have proper feeding ability as a result their body and immune system is much weaker as compared to normal babies of their age (Chaudhry*et al* ., 1996).Sieges is the serious most attack of any organism or pathogen on these babies because their immune system is too weak to fight with those pathogens. Loss of hearing is the condition in the patients of zellweger syndrome that their hearing ability decreased or completely lost. Decrease or complete loss of vision is also a worst side effect of this disease and patients suffering of this disease may lost their vision. Strange or uncommon facial features is also one of the most important characteristic of patients of zellweger syndrome that they have peculiar facial features and have odd look overall. Some skeletal disorders are also present in the patients of zellweger syndrome disease that they have weak skeletal system as compared to normal babies (Berendse*et al* ., 2014).

Childrens suffering from this mostly have also different serious abnormalities in other body organs and these other body organs and tissues may include liver, heart and kidneys. Childrens who are patient of disease zellweger syndrome mostly survive upto one year of life and do not live more than one year mostly.The most common and well known cause of zellweger syndrome is the mutation in anyone gene amongst 12 genes but mainly due to the mutations in PEX1 is related to it (Mignarri*et al* ., 2012).The manner of inheritance of zellweger syndrome is autosomal recessive. Till now there are no specialized or specific cures for this disease. Treatment for this disease is on the basis of symptoms and support system. We can say that it is a genetically heterogenous disease which is caused due to the result of mutations in several genes called ‘pexins’ and these pexins are involved in biogenesis of peroxisome. These pexins genes are most commonly used in the coding of proteins which are compulsory for the assemblage of peroxisomes (Poll and Gartner ., 2012).

The most common types of zellweger syndrome consisted of;

PBD1A which is caused due to the mutation of PEX 1 gene, on chromosome no. 7.PBD2A which is resulted due to the mutation in PEX 5 gene, on the chromosome no.12. PBD3A which is caused due to the mutation of PEX 12 gene, on the chromosome no. 17. PBD4A which is resulted due to the mutation in PEX 6 gene, on the chromosome no. 6. PBD5A which is casued as a result of the mutation on PEX 2, on the chromosome no. 8. PBD6A which is resulted due to the mutation in PEX 10, on the chromosome no. 1. PBD7A which is mainly as a result of the mutation in PEX 26, on the chromosome no. 22. PBD8A which is resulted as a result of the mutation in PEX 16, on the chromosome no. 11. PBD10A which is caused due to the mutation in PEX 3, on the chromosome no. 6. PBD11A which is mainly due to the mutation in PEX 13, on the chromosome no. 2. PBD12A

which is resulted due to the mutation on PEX 19, on the chromosome no. 1. PBD13A which is caused due to the mutation in PEX 14, on the chromosome no.1 (Moser *et al* ., 1995).

The prognosis for this disease is very bad, a large number of infants even fail to live the six months of their lives, and usually they fail to survive due to gastrointestinal bleeding, respiratory disorders and liver disease. There is not any standard course of treatment for zellweger syndrome. NINDS and NIH named institutes are working on it and trying to find out treatment for this disease. The main aim of their research is to understand the complete mechanism of zellweger syndrome and then finally to discover a cure for it (McMillan *et al* ., 2012).

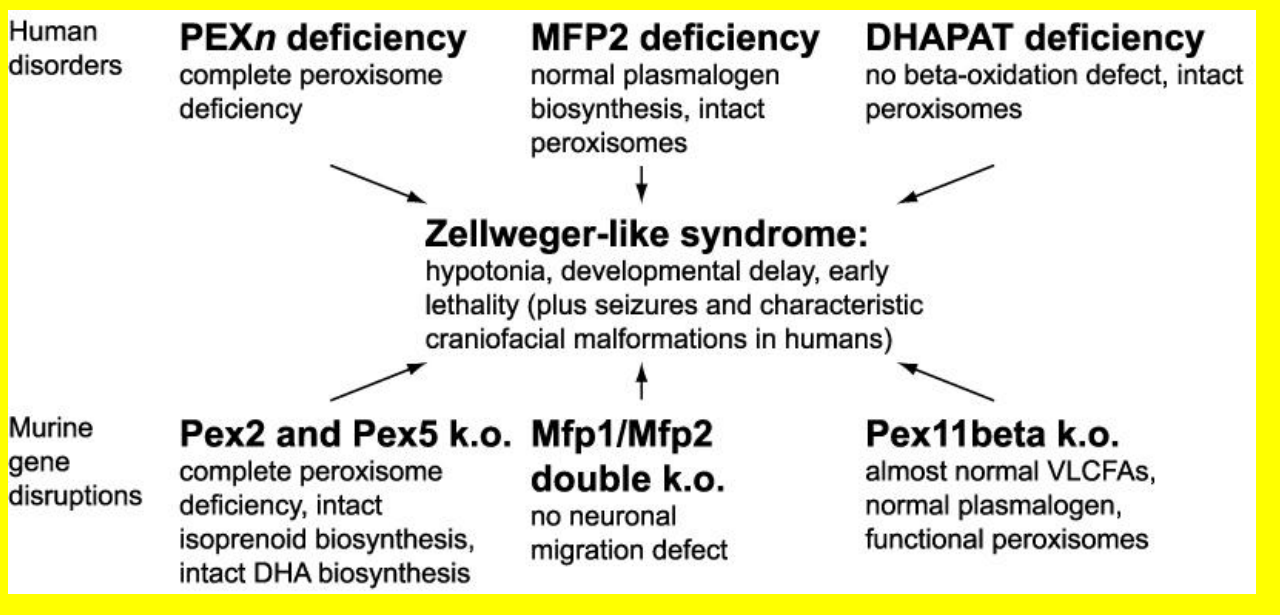

Figure: deficiencies of PEXn, MFP2, DHAPAT and murine gene disruptions related to zellweger syndrome

DISEASE NAMES AND SYNONYMS

Zellweger spectrum disorder, Zellweger syndrome spectrum, Zellweger syndrome, Neonatal adrenoleukodystrophy, Infantile Refsumdisease ,Heimler syndrome (Lines *et al* ., 2014).

CAUSES

Zellweger spectrum disorder is an autosomal recessive disorder. It is due to the mutations of almost 13 PEX genes,autosomal recessive disorder means this is just one of many different ways can be passed down into families. When we say this person is effectd of zellweger syndrome its mean in this patient there is almost two copies of mutant or an abnormal genes which are responsible for this

disorder (Kocur and Resnikoff ., 2002).These PEX genes are responsible for the proper functioning of peroxisomes.This disease is related to the reduction or lack of peroxisomes. In the consequence of reduction of peroxisomes the metabolic pathways which are related by peroxisomes gets disturb. Peroxisomes are the structure which are responsible for lipid production which are helpful to digestion and in proper breakdown of fatty acids and metabolic pathways which takes place within body (England *et al* ., 2005).

These chemical processes are responsible for proper functioning of body .in anabolic as well as in catabolic pathways peroxisomes are involved, e.g biosynthesis of bile acids and ether phopholipids, fatty acids oxidation(α and β oxidation) as well asglyoxylate detoxification and the reactive oxygen species. That's why in tissues there are biochemical problems arises due to malfunctioning of peroxisomes. Almost 60% chances of zellweger spectrum observe in patients Due to mutant PEX1 gene,and there may be 90% mutations in PEX1 (Dacremont and Vincent ., 2010). There are almost 12 PEX mutants genes are known for this disorder butthereare many different genes responsible for this. (PEX1,PEX2,PEX3,PEX5,PEX6,PEX10,PEX12,PEX13,PEX14,PEX16,PEX19,PEX26). The patient of zellweger syndrome has mutant genes and these infants may accumulate;

Very long chain fatty acids(VLCFA)

Branched chain fatty acids(BCFA)

These fatty acids into their tissues and in cells. The accumulation of these fatty acids may cause C.N.S damaging especially myelin(hypomyelination), hepatomegaly, hypoplastic, chondrodysplasia punctuate and hypotonia etc. brain and lungs functioning also disturb because the low level of plasmalogens as well as low level of ether phospholipids. If the parents is carrier means they have affected one out 12 PEX genes the newborn baby have almost 25% chances to develop this disease that's why genetic councsling is very important before giving birth.it has been noticed that with each pregnancy a women has one chance out of 4 chances (Ferdinandusse*et al* ., 2006).

SIGNS AND SYMPTOMS

There are many symptoms of zellweger syndrome which may vary from one individual to another , and in affected infants the specific numbers and severity of this syndrome also different. The sever form noticed shortly after birth. These infants develop life threating conditions during their first year of life. The symptoms of this disease appear after few hours or after few days of birth (Leivesque*et al* ., 2012).

Clinical symptoms

facial symptoms.

Table: signs and Symptoms and their frequencies in zellweger syndrome patients

Signs and symptoms	Approximate number of patients
High forehead	Very frequent (80-99%)
Jaundice	Very frequent (80-90%)
Respiratory insufficeny	Very frequent (80-90%)
Flat face	Very frequent (80-99%)
Feeding difficulties	Very frequent (80-90%)
Cataract	Frequent (30-79%)
External ear malformation	Very frequent (80-99%)

Clinical symptoms include: autoimmune or autoinflammatory disease, hypotonia(a condition of poor muscle), feeding difficulties as well as have poor sucking capabilities, seizures, dysfunctioning of liver , liver cysts, vision loss and hearing loss, macrocephaly (infants with large head) and microcephaly(infants with small head) are also reported. Eyes disease include cataracts another eyes disease nystagmus (it is a fast movement of eyes), Glaucoma, jaundice also reported in such infants , also they have no ability to move, gastrointestinal bleeding increased level of copper and iron in blood, intellectual disability and parental growth failure (Matsui *et al* ., 2013).

Facial symptoms include peculiar facial features. Patients of zellweger syndrome have trampled face characteristics their nasal passageway is also wide as compared to the normal ones. The patients have odd forehead too. They also have space between the ends of their eyelids. The eyebrow ridges of the patient babies are also not normal and are under development. Their eyes are wide- set too. Facial symptoms are not limited only to these odd characteristics but patients suffering from zellweger syndrome have many other distinct facial features and also have skeletal and muscular abnormalities (Pierce *et al* ., 2010). The patients have large space present between their bones which adds to the oddness and peculiarity of the patient babies.Flattened face and these distinct facial

features are characteristic of patients of zellweger syndrome and also include broad nasal bridge, high forehead, having space between the margins of eyelids, with epicanthalfolds , the fold of skin of an upper eyelid which is over both or one of their inner angles of eyes,underdeveloped eyebrow ridges, wide set eyes, forward tilting nostrils,smaller lower jaw and minor ear anomly (Ebberink*et al* ., 2012).

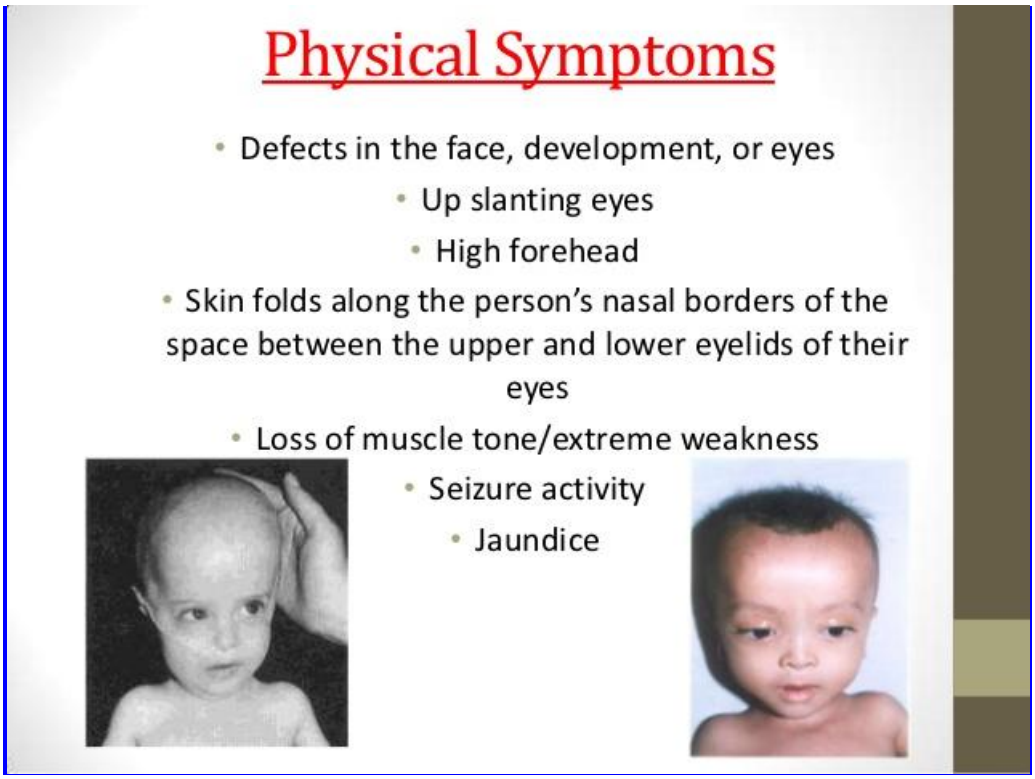

Figure: physical symptoms including facial, skin and muscles disorders related to zellweger syndrome

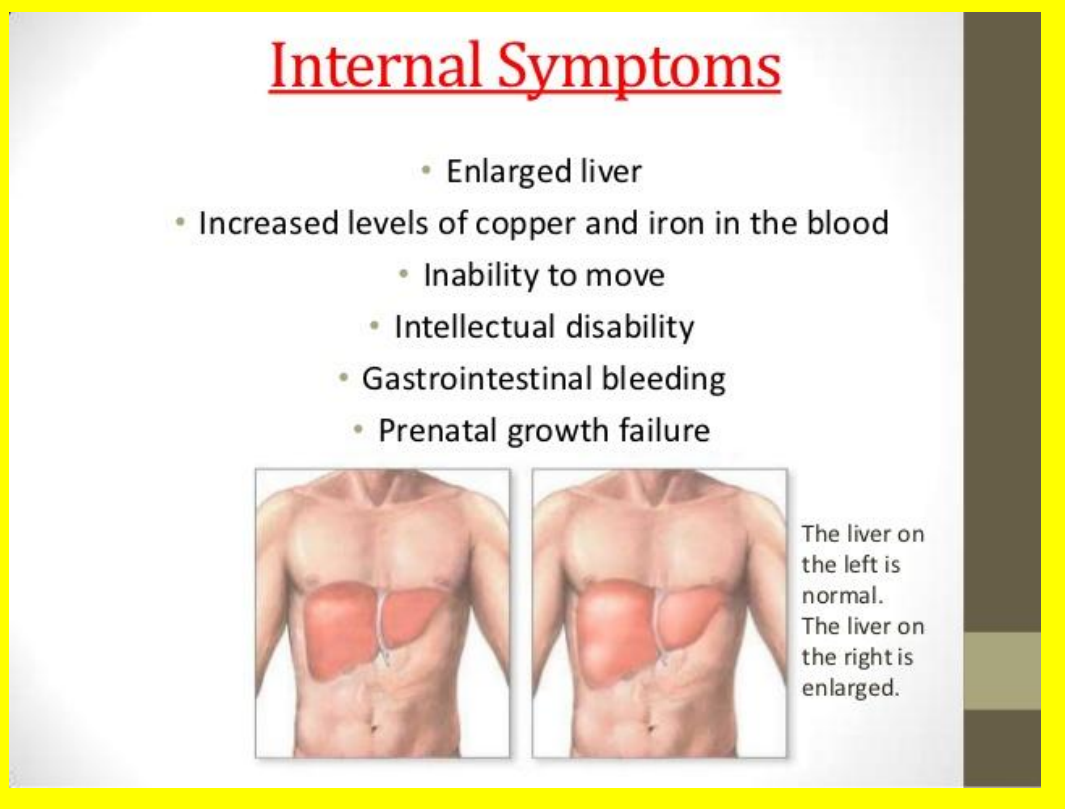

Figure: Internal symptoms related to zellweger syndrome

EPIDEMIOLOGY AND LIFE EXPECTANCY

The chances of occurance of zellweger syndrome is about 1 in 50,000 newborn babies in US. It is presumed that ZSDs occur worldwide, but the incidence may differ between regions.it had been thought that this disease has been spread world wide but there chances of incidence vary from region to region. e.g in case of French-Canadian region the chances of occurance of this disease just about 1 in 12 and in Japan low chances of incidence that is 1 in 50,000 (Gootjes*et al* ., 2002). The exact level or exact percentage of occurance of xellweger syndrome will become available after the development of X-linked adrenoleukodystrophy in many countries.Due to its congenital natureand the rate percentage at which the functions of peroxisomes disturb such as(demyelination), the treatment as well as prognosis for affected infants is very poor. The life expectany of such affected children thought to be less than 6 months they died due to liver damaging or respiratory system failure and brain damaging (Hibler*et al* ., 2014).

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INHERITANCE PATTERN

This condition is acquired in an autosomal latent example, which implies both duplicates of the quality in every cell have transformations. The guardians of a person with an autosomal passive condition each convey one duplicate of the changed quality, however they normally don't give hints and side effects of the conditi. If both parents are carrier then there is a chance that there child may also have this syndrome there are 25% chances that they may have chance to have this risk, and chance to be carrier like parents is 50% (1 in 2) and 25%chance may be they have syndrome or may be not (Bowen et al ., 1964).

CLINICAL FEATURES

ZSD patients divided into 3 groups on the base of age of presentation

Neonatal-infantile presentation

Childhood presentation

Adolescent presentation

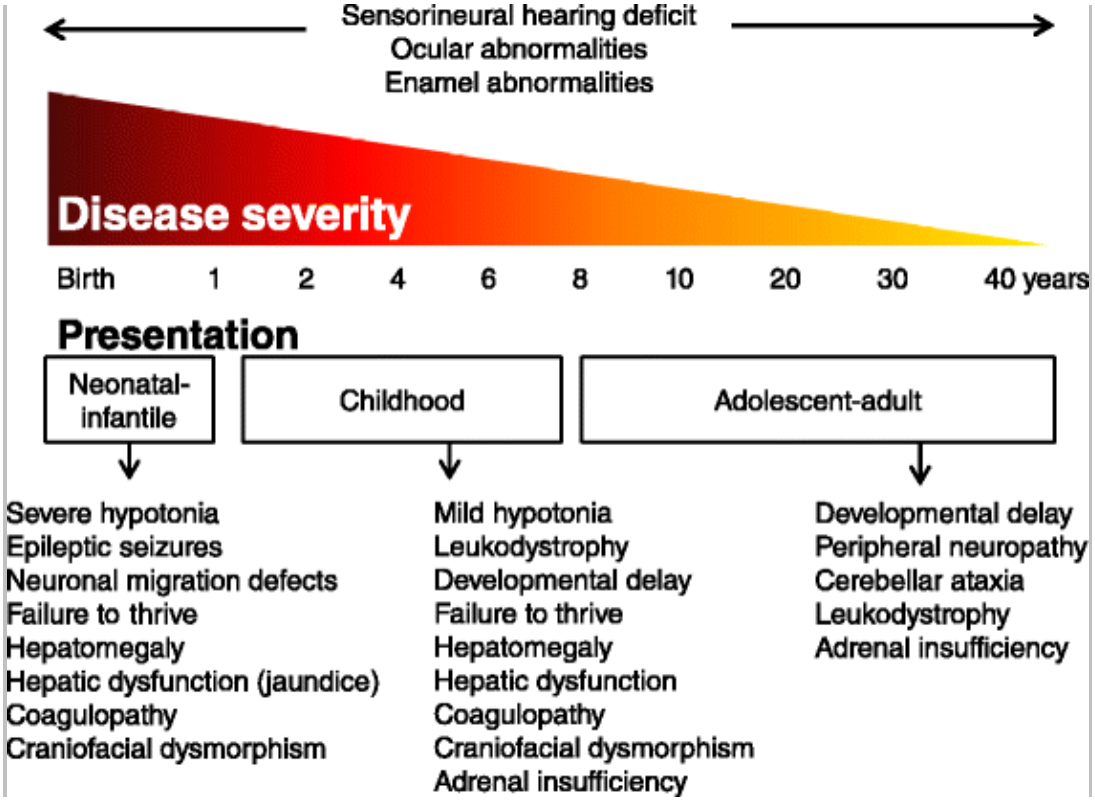

Figure: Schematic overview of main presenting symptoms in ZSDs per clinical group

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Neonatal-infantile presentation:

Patients of ZSD especially in their neonatal period face hepatic dysfunction and hyptonia (muscle loss) result in jaundice as well as in feeding difficulties. In these patients epileptic seizures(uncontrol and unconscious movement of muscles),present. Abnormal feqatures are found especially the most prominent facial dysmorphic characteristics. Eyes abnormalities(cataracts,glaucoma and retinopathy) sensorineural deafness but these dysfunction features are not prominent during this presentation. Neocortical dysplasia shown by MRI which matter volume decreased, myleinationbilaterial ventricular dilation delayed. Onset of leukodystrophy is described rarely in neonatal-infantile. In knees and hips calcific stippling related to chnodrodysplasia may present. In this presentation survival is not more than one year and poor prognosis (Moser ., 1999).

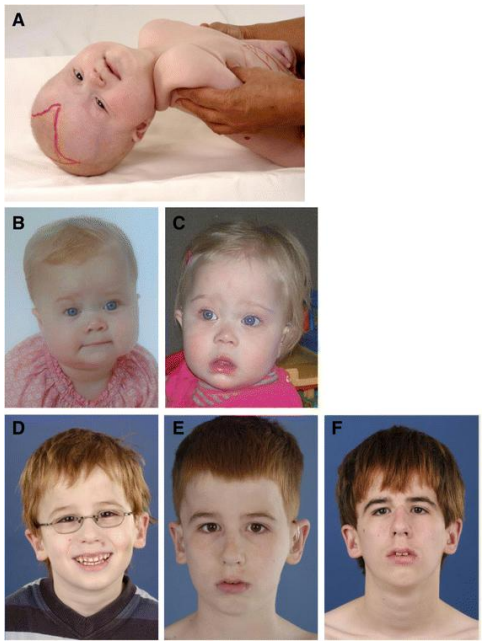

Figure: Craniofacial dysmorphic features in ZSD patients developing over time

Childhood presentation

In this presentation the symptoms are widely different from those that were present in neonatal-infantle presentation. In this presentation tunnel vision and early blindness takes place due to eyes abnormalities(cataracts, retinitis pigmentosa, glaucoma). Craniofacial dysmorphic features less pronounced as compared to neonatal-infantile presentation. In childhood presentation adrenal insufficeny and renal calcium oxalate may be develop (Peters ., 1961).

Adolescent-adult presentation

In this group less severe symptoms are present and diagnosis possible in late age or in adulthood. The most prominent symptoms are ocular abnormalities as well as sonsorineural hearing deficit. Craniofacial dysmorphic(related to face+skull abnormalities)present, can also be absent. Symptoms may vary from affected patients to patientse.g, delay in development variable different among different patients but in some patients intelligence remains unaffected. The primary adrenal insufficiency isz most common and most probably under diagnosed. There are other neurological abnormalities also present in addition to delay in development e.g , cerebellar ataxia, signs of peripheral neuropathy as well as pyramidal tract signs. Slowly progressing takes place and disease become stable for many years (Gould *et al* ., 2001).

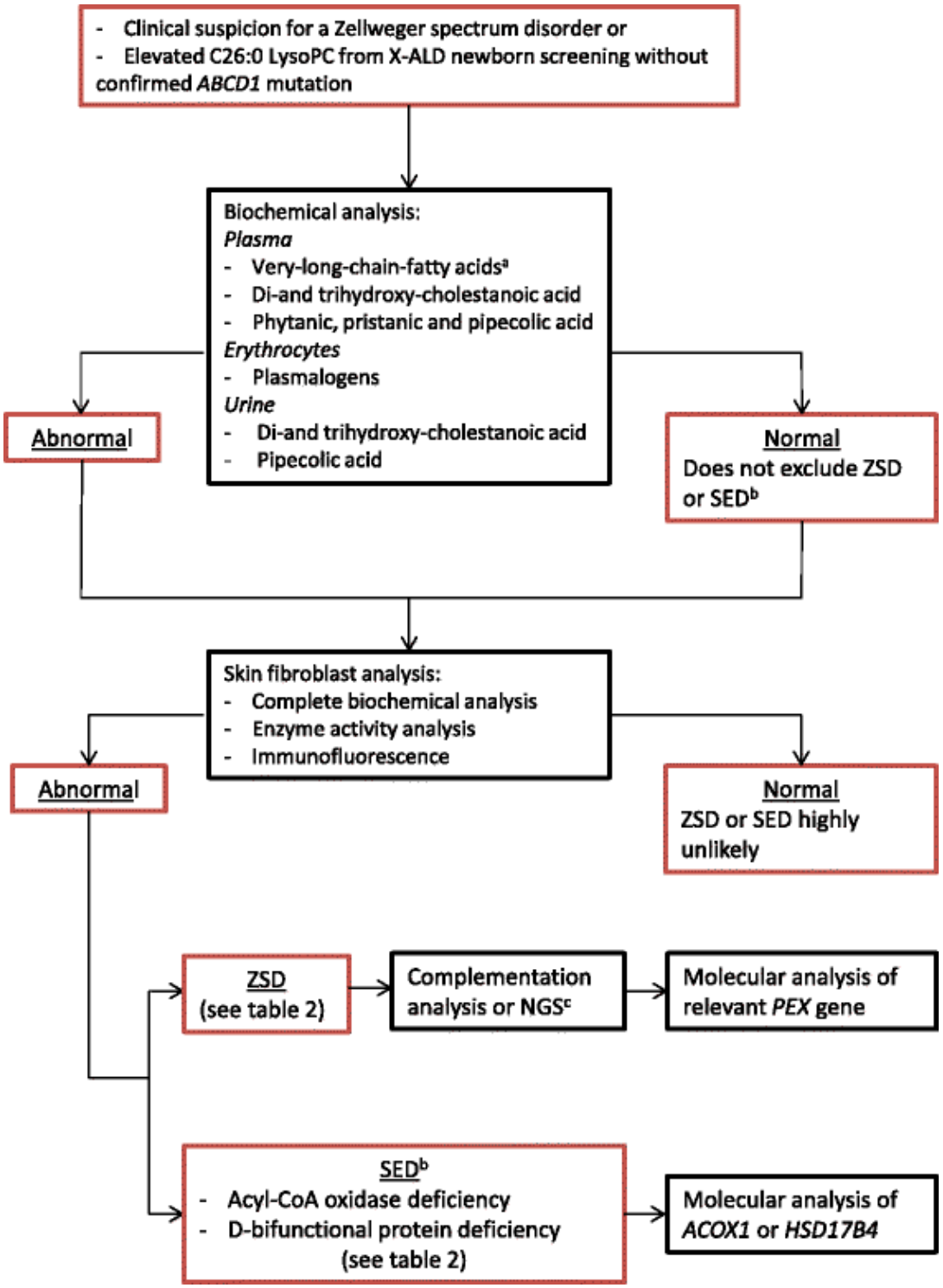

Figure: Diagnostic flow-chart for ZSDs.

GENETIC COUNSELING AND ANTENATAL DIAGNOSIS

As a result of the poor result and high ailment load related with the larger part of ZSDs, hereditary advising ought to be offered to guardians of influenced kids. Bearers can be offered pre-birth or preimplantation hereditary determination. Before pre-birth hereditary testing can be played out the familial pathogenic transformation in one of the PEX qualities require to be recognized (Ebbering*et al* ., 2011). On the off chance that the PEX transformations are obscure or can't be recognized, biochemical pre-birth testing for ZSD is conceivable in chorionic villus biopsy material, refined chorionic villus cells or refined amniocytes. Biochemical pre-birth testing must be performed if there should be an occurrence of clear biochemical irregularities in cells from the list understanding.Hereditary advising proposed to guardians of an influenced childrens, transporters of this disorder offered either parental finding or perimplantation hereditary analysis (Pool *et al* ., 2004).

Diagnosis

Different genetic tests are commonly used for the purpose of diagnosis of zellweger syndrome disease but in recent times biochemical tests have also shown great effective results for the diagnosis of zellweger syndrome disease. We digonsed patients of zellweger syndrome disease on the basis of high level of very long fatty acids chain present in their plasma of blood.Sometime we misdiagnosed zellweger syndrome disease with other diseases because the symptoms of this disease show similarity with different other diseases. Hence the newly diagnosed patient should confirm via tests that the diagnosis of diseases is correct or not.. There should be proper testing of disease to avoid chances of misdiagnosis so that we can start treatment of our disease (Dacremond*et al* ., 1995).

Diagnosis of zellweger syndrome is suspected when the signs of disease start showing from birth especially the distinguishing facial features. We mostly employ those tests which are used to identify peculiar substances in urine and blood. We can also use biochemical analysis for diagnosis of zellweger syndrome disease (Foucher*et al* ., 2006).

BIOCHEMICAL ANALYSIS

For secreening of functional peroxisomes we use few markers. Because peroxisomes are involved in oxidation of very lox chain fatty acids and branched chain fatty acids if there is high level of these fatty acids in a body this threshold level gives indication of zellweger syndrome... VLCFA and plasmalogen parental analysis examples which are used from amniotic tests. High level of VLCFA in plamsma as well as in liver biopsy the peroxisomes absence are the signs of zellweger syndrome. The extension of this in the urine of ZS patienets there are high level of arachidonic acids metabolites excreted (Rass-Rotshchild*et al* ., 2002).

TREATMENT

Currently there is no cure and good treatment till discovered for the thezellweger syndrome but in most of cases mentioned treatments are suggested for the patients of zellweger syndrome are; Cholic acid, Docosahexaenoic acid, Lorenzo's oil, Plasmalogen precursors, Citrate, Supportive care (Shaheen*et al* ., 2011). Brief description of above mentioned treatments is given below;

Cholic Acid

In different cases, reports have showed favourable result of cholic acid in babies who are patients of zellweger syndrome disease. The only limitations to the treatment of zellweger syndrome by using cholic acid are the small number of babies and short follow-up. The provided evidence is not sufficient to say that either cholic acid usage for treatment of zellweger syndrome is beneficial or not for the patients of zellweger syndrome disease. In united states the food and drug administration has recently confirmed that the use of cholic acid is safe for the treatment of patients (Wanders*et al* ., 1995).

Docosahexaenoic Acid

Docosahexanoic acid plays a vital role in proper functioning of retinal and nervous system. As patients of zellweger syndrome disease have low level of DHA present in their membranes of WBCs and the Tetracosahexanoic acid do conversion of peroxismal to DHA and the patients of zellweger syndrome are suggested to have supplementation of DHA as a possible treatment (Steinberg *et al* ., 2006).

Lorenzo's Oil

The therapy involving use of lorenzo's oil was basically started for the treatment of single peroxisomal enzyme deficiency and it was observed that it lowers VLCFAs in plasma, but it was not found much effective on progression of disease (Wanders et al ., 1995).

Plasmalogen Precursors

We know that the patients of zellweger syndrome disease may not have sufficient levels of plasmalogens, so the proper supplementation of plasmalogens in the form of plasmalogen precursors is necessary for the patients of zellweger syndrome disease because plasmalogens play a vtal character in cell membranes and also act as anti-oxidants. This has effective result on patients (Steinberg *et al* ., 2006).

Citrate

Oxalate metabolite is very toxic in nature and it starts to accumulate in plasma and urine from patients of zellweger syndrome disease. This accumulation of toxic oxalate results in the formation of calcium oxalate stones. And patients of zellweger syndrome disease have approximately largest percentage 83% of calcium oxalate stones which is very fatal for them. In order to avoid accumulation of oxalate and prevention of calcium oxalate stone production, oral citrate treatment is suggested (Wanders*et al* ., 1995).

SUPPORTIVE CARE

There should be proper screening of patients of zellweger syndrome disease forEpilepsy, Enamel hypoplasia, Adrenal insufficiency, Hearing impairment, Visual impairment, Vitamin K dependent coagulopathy, Low levels of fat soluble vitamins, High levels of phytanicacid.We should treat the patients according to their abnormalities. Patients should be *treated only due to exact or true insufficiency and not on the basis of minute deficiencies (Weller et al* ., 2003).

CURRENT AND FUTURE DEVELOPMENTS

A few intensifies that animate peroxisomal biogenesis and capacity in vitro were found as of late and clinical trials are progressing. Ideally, some of these mixes will have the capacity to protect or enhance peroxisomal work in patients. The best valuable impact is normal in patients whose fibroblasts demonstrated a temperature affectability with declining of the phenotype when refined at 40 °C and change of peroxisomal capacities at 30 °C. Notwithstanding these new exacerbates, the impact of cholic corrosive is at present under scrutiny in a substantial partner of ZSD patients (Vreken*et al* ., 1998).

Albeit never tried in ZSD patients, quality treatment with or without tissue particular focusing on may be a potential treatment. Quite a long while back quality treatment was at that point proposed for X-ALD. Albeit promising, quality treatment still should be enhanced to be doable for patients . To begin with, studies must be directed in the as of late distributed mellow PEX1 mouse demonstrate, before a human trial can be started.Anorthotopic liver transplantation was described in a single 6-month old ZSD patient and hepatocytes transplantation in another 4-year old patient .It resulted in decreased concentrations of VLCFAs and pipecolic acid, and improved bile acid profiles. However, the effect on long-term disease course has not been reported (wanders *et al* ., 1995).

Albeit bone marrow transplantation (BMT) is a set up treatment for the cerebral youth type of X-ALD, there are no reports depicting BMT in ZSD patients. BMT would be of enthusiasm for those patients who create leukodystrophy in earliest stages. Be that as it may, with the present learning it is

difficult to anticipate if patients will build up this quick dynamic adrenomyelopathy phenotype after BMT. In any case, BMT could be gainful for a subgroup of patients inside the ZSD range, yet first new systems/markers that can foresee regardless of whether patients will build up an extreme dynamic leukodystrophy must be elucidatedleukodystrophy. As of late, a review think about uncovered that patients with X-ALD still build up an (Dacremont*et al* ., 1995).

PROGNOSIS

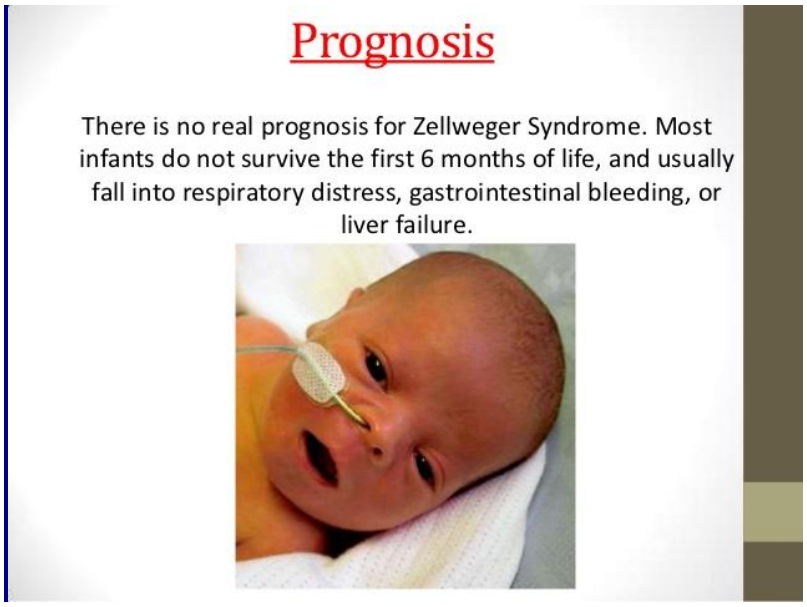

Figure: 6 prognosis for zellwegersyndrome

In spite of the fact that a harsh genotype-phenotype relationship exists for a few PEX qualities, for example, PEX1 and PEX26 .the seriousness and movement of the sickness is hard to anticipate for individual patients. This will turn out to be more important as infant screening is actualized. As an outcome of infant screening for X-ALD by C26:0-lysoPC in a few nations ZSD will likewise be analyzed during childbirth. Kids with the extreme phenotype (neonatal-puerile introduction with serious clinical side effects) have a poor forecast and these patients as a rule pass on inside the main year of life (Hibler*et al* ., 2014).

Patients that present in youth or puberty as a rule have a superior anticipation, however can create dynamic liver illness or leukodystrophy and break down. On the off chance that dynamic liver infection or leukodystrophyhappens guess is poor. The staying milder people can achieve adulthood without movement or with long stretches of adjustment. At the point when movement happens, it is for the most part identified with fringe neuropathy and pyramidal signs, while cognizance stays stable.(Foucher*et al* ., 2006).

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