DOWNLOAD PDF PEROXISOMAL DISEASES

Chapter 1 : Peroxisomal Disorders | www.nxgvision.com

Peroxisomal disorders are a group of genetically heterogeneous metabolic diseases that share dysfunction of peroxisomes. Peroxisomes are cellular organelles that are an integral part of the metabolic pathway. They measure about Âµm in diameter and can differ in size between different species.

Kunihiko Suzuki and Marie T Vanier. This group comprises neurological disorders that occur as the result of defects in biogenesis of peroxisomes or, directly or indirectly, in enzymes that are normally localized in peroxisomes. For an overview of this rapidly evolving field, readers are referred to review articles [1 , 3 , 24 â€" 27]. In the following, only representative disorders are described. Table summarizes the main biochemical abnormalities and the known genetic defects in these diseases. Disorders of function can result from genetic defects in factors that are critical for peroxisomal formation These disorders form a clinically and genetically heterogeneous group of severe autosomal recessive diseases [26]. Consequently, peroxisomes are either absent or abnormal morphologically, and there is a general failure of all metabolic functions normally associated with the peroxisome. The term Zellweger spectrum ZS has been given to a complex group of disorders with overlapping clinical features and common biochemical abnormalities [28]. However, it should be emphasized that this classification is based on clinical phenotypes but not on genetic causes. The metabolic abnormalities common among these disorders include accumulation of very long-chain fatty acids VLCFA and of phytanic acid, elevated bile acid intermediates and deficiency of plasmalogen biosynthesis. Peroxisomes are virtually absent in hepatocytes and fibroblasts, although peroxisomal membrane ghosts can be found. In spite of this common biochemical phenotype, genetic complementation analysis using cell hybridization has revealed the existence of at least nine different complementation groups CGs , with no correlation to any given clinical phenotype. This clearly indicates the complexity of peroxisome biogenesis and of the genetic disorders that can result from abnormalities in any of the steps. The prototype of the generalized peroxisomal disorder is ZS , or cerebro-hepato-renal syndrome, in which the seminal discovery of an apparent lack of peroxisomes in hepatocytes and renal tubules was made quite early. Patients show a combination of craniofacial dysmorphia; neurological abnormalities, including pronounced hypotonia, epileptic seizures and severe psychomotor retardation; ocular abnormalities; and liver involvement. They die before the end of the first year. The brain shows micropolygyria. The most characteristic neuropathological abnormality is an impaired neuronal migration and severe demyelination. The first described patient with this disorder showed central demyelination and adrenal atrophy, hence the denomination, together with abnormalities similar to those seen in ZS , although milder. IRD patients show no distinct abnormalities in the neonatal period and only minor dysmorphia. The main clinical features are mental retardation, retinitis pigmentosa, neurosensory deafness and growth retardation. Several reported patients were still alive in their late teens. Rhizomelic chondrodysplasia punctata RCDP. The characteristic clinical features of this disorder are rhizomelia: Biochemical peroxisomal abnormalities consist of a severe deficiency of plasmalogens, with combined deficiency of dihydroxyacetone-phosphate acyl-transferase DHAP-AT and alkyl- DHAP synthetase. Peroxisomes are present but abnormal. In disorders of peroxisomal biogenesis, an apparent lack of abnormal appearance of peroxisomes and mislocalization of several peroxisomal matrix proteins suggest a problem of protein import as the primary lesion. Considerable progress has been achieved in this field. Peroxisomal targeting signals, either C-terminal PTS1, for most proteins or N-terminal PTS2, for thiolase and other yet unknown proteins have been discovered and proteins involved in peroxisomal import, biogenesis, proliferation and inheritance isolated. The concerted action of such peroxisomal assembly proteins, peroxins, has been shown to govern import of matrix proteins into peroxisomes, and many of the corresponding PEX genes have been cloned, at least in yeast [29]. To date, defects in at least five PEX genes have been shown to cause human peroxisomal disorders. The name adrenoleukodystrophy was coined based on the features of a progressive genetic demyelinating disease associated with adrenal insufficiency manifesting in boys aged 5 to 13 years. Different phenotypes are commonly observed in the same family or the same kindred. Initial behavioral and school problems are followed by gait disturbances, visual and hearing impairment, varying

alterations of cognitive functions with progressive dementia and a devastating downhill course toward an apparent vegetative state in 3 to 5 years. Most patients die in adolescence. Severe and confluent demyelinating lesions involving the parieto-occipital region are observed most characteristically, but magnetic resonance imaging MRI studies have shown other topographic localizations, especially at an early stage of the disease. Correlations between the initial localization of demyelinating lesions and progression of the disease have been reported. A rare adult-onset cerebral form has been described. This form involves predominantly the spinal cord and peripheral nerves with the main clinical symptoms of spastic paraplegia and adrenal insufficiency, and the disease progresses slowly over decades. Some degree of cerebral involvement may occur in one-third to one-half of patients, as judged by brain MRI and cognitive functions. A significant proportion of female carriers show varying degrees of clinical signs of the disease. These fatty acids are present mostly in the forms of cholesterol esters, cerebrosides, gangliosides and sphingomyelin. There are no indications of other peroxisomal dysfunctions. The biochemical pathogenesis that leads to the massive demyelination is unclear because, even though the relative increase is large, the net concentrations of VLCFA in the tissue remain very low. Elucidation of its precise physiological function should provide insight into the pathogenetic mechanism of this disorder. More than disease-causing mutations have been described. A murine model has been generated [31]. There is an abnormal elevation of a methylated fatty acid, phytanic acid, which is exogenously derived from chlorophyll in the food. There is no indication of other peroxisomal dysfunction. Peroxisomes appear morphologically normal in size and number. Since phytanic acid is exclusively exogenous in origin, chlorophyll-free dietary treatment can be quite effective in alleviating the disease. By agreement with the publisher, this book is accessible by the search feature, but cannot be browsed.

Chapter 2 : Peroxisomal diseases

Peroxisomal disorders represent a class of medical conditions caused by defects in peroxisome functions. This may be due to defects in single enzymes [2] important for peroxisome function or in peroxins, proteins encoded by PEX genes that are critical for normal peroxisome assembly and biogenesis.

Goldstein has had a special interest in neurogenetic and neurometabolic disorders since her Pediatric intern year. She has received several awards for patient satisfaction, including Best Doctors in Pittsburgh Magazine. She has contributed to recent literature on the diagnosis, management, and consensus criteria for mitochondrial disease. Her current interests are in conducting clinical trials for patients with genetically confirmed mitochondrial disorders. These conditions vary in symptoms and age of onset. However, they share a problem with the functioning of the peroxisome. Peroxisome is a small organelle within the cell. Some of the issues are break-down beta-oxidation of very long chain fatty acids in the peroxisome, hydrogen peroxide detoxification, and the synthesis production of cholesterol, bile acids, and plasmalogens. Because myelin production can be disrupted in some of these disorders, they are also classified as white matter disorders. White matter disorders are called leukodystrophies. The hallmark of peroxisomal disorders is an accumulation of the very long chain fatty acids 24 and 26 carbons long C24, C26 as well as accumulation of bile-acids. There are four main groups of peroxisomal disorders based on clinical symptoms: Different genes have been discovered to play a role in peroxisomal fatty acid metabolism; mutations in these genes cause PBD-ZSS. Older children may have visual and hearing impairment. The second category involves mainly bone dysplasias called rhizomelic chondrodysplasia punctata RCDP and will not be discussed here. X-linked disorders affect males more than females; females are asymptomatic carriers with some few exceptions. X-ALD affects the white matter of the brain and the adrenal glands which are near the kidney. The childhood form of X-ALD begins between years old with attention deficit hyperactivity disorder ADHD , followed by cognitive decline, behavior issues, loss of vision and hearing, and motor decline. The progression to disability is rapid, often within 2 years. The fourth category is Adult Refsum disease. Onset of symptoms can be in the first year of life to late adulthood. Symptoms include blindness due to retinitis pigmentosa , deafness, balance issues ataxia , and a skin condition called ichthyosis. Symptoms progress to include heart issues including cardiomyopathy an enlarged heart. X-ALD affects older children by causing attention and behavior issues, followed by major and rapid regression in cognitive and motor abilities, and then by loss of vision and hearing. The child becomes spastic and unable to control their movements within a few years of symptom onset. Symptom severity in PBD-ZSS ranges from children who gain very few milestones severe and never learn head control or how to roll or sit. At the mild end of the severity spectrum, children may learn to walk, talk and gain early education skills. Symptom severity in X-ALD ranges from devastating course in childhood, to a milder form presenting later in life, or symptoms limited to the adrenal gland. There is currently no cure for these disorders, and care is palliative. X-ALD is also an incurable disease. For X-ALD, the diagnosis is based on the typical clinical symptoms in boys. MRI is abnormal and characteristic for X-ALD with white matter disease that starts in the back of the brain near the occipital lobes. Genetic testing can be performed on the ABCD1 gene for the associated mutation. Adult Refsum disease is diagnosed based on symptoms and elevated phytanic acid levels. Common symptoms of PBD-ZSS include global developmental delays delays in gross motor, fine motor, language , hypotonia, hearing and visual impairments. Symptoms may be present in the newborn period, older childhood, and even adulthood. In the newborn period, symptoms include: Hypotonia low muscle tone with poor feeding Seizures Liver dysfunction may cause neonatal jaundice and increased liver enzymes testing in blood Facial features which may be seen early in life, such as a large open fontanelle, broad nose, and a high forehead with a flattened face Bones x-ray may show bone stippling, called chondrodysplasia punctata Brain imaging may reveal cortical dysplasia, also called migrational abnormalities, due to abnormal formation of brain architecture referred to as pachygyria-polymicrogyria. The brain malformations correlate with the severity of seizures and developmental delay as well as the elevation in very long chain fatty acids and bile-acids. Older children have milder symptoms at presentation, and may include:

Hearing loss which may be the first sign Developmental delay Low muscle tone Liver dysfunction which may lead to abnormal bleed and be the first sign of the disorder Retinal dystrophy abnormal retina of the eye. Presenting as an adult would be very rare for these disorders, but it has been reported in the medical literature. Usually those individuals have had only nerve involvement causing numbness and tingling and have had PEX6 deficiency. Adult Refsum disease presents later in life, with symptoms such as: Balance issues ataxia Retinitis pigmentosa abnormal pigmentation of the retina of the eye Hearing loss Peripheral nerve disease Physical Abnormalities A child with PBS-ZSS and X-ALD, among other conditions, may have epilepsy, developmental delay, cerebral palsy, visual impairment and deafness. Other findings include abnormal brain architecture cortical dysplasia and cysts in the germinal matrix. White matter abnormalities might be seen on certain sequences diffusion-weighted imaging and diffusion tensor imaging: Imaging of X-linked adrenoleukodystrophy shows white matter disease in the posterior brain occipital lobes but can start in the front of the brain. The white matter abnormalities will spread to involve the remainder of the brain over time. Biochemical testing includes very long chain fatty acids VLCFA , phytanic acid, pristanic acid and plasmalogens. VLCFA entails measuring long carbon chain fatty acids and examining their ratios to each other. An elevation of C C22, is consistent with a peroxisomal disorder. Phytanic acid is present in our diet in dairy products, meat and fish. It is also a fatty acid which undergoes metabolism in the peroxisome by first being converted to pristanic acid. Pristanic acid is then converted to medium chain fats that are further metabolized by the mitochondria. Elevations of phytanic and pristanic acid are seen in dysfunctional peroxisomes and can be an indication of adult Refsum disease. Plasmalogens are synthesized made in the peroxisome. Testing for plasmalogens may reveal a deficiency in X-ALD and Zellweger syndrome due to impaired plasmalogen biosynthesis. Other testing may involve an electroencephalogram EEG to detect seizures. The biochemical testing is usually covered by insurance. Genetic testing for confirmation of mutations in involved genes may vary based on insurance companies. Even if initially denied, your doctor may be able to write a letter of appeal stating the importance of confirming the diagnosis so that proper treatment and prognosis may be offered to you. The biochemical tests do not need to be repeated. Audiology for hearing evaluations.

Chapter 3 : Peroxisome - Wikipedia

The peroxisomal membrane is a lipid bilayer with embedded peroxisomal membrane proteins. All peroxisomal membrane proteins and enzymes of the peroxisomal matrix are encoded by nuclear genes, synthesized on free ribosomes, and imported into the peroxisomes.

The following algorithms are available in Special Instructions: Increased Very Long Chain Fatty Acids Clinical Information Discusses physiology, pathophysiology, and general clinical aspects, as they relate to a laboratory test Lysosomes are intracellular organelles that contain hydrolytic enzymes to degrade a variety of macromolecules. Lysosomal storage disorders are a diverse group of inherited diseases where macromolecules accumulate due to defects in their transport mechanisms across the lysosomal membrane or due to defective lysosomal enzyme function. Accumulation of these macromolecules in the lysosomes leads to cell damage and, eventually, organ dysfunction. More than 40 lysosomal storage disorders have been described with a wide phenotypic spectrum. Gaucher disease is an autosomal recessive lysosomal storage disorder caused by a deficiency of acid beta-glucosidase glucocerebrosidase: GBA resulting in increased storage of glucocerebroside D-glucosylceramide. The deposition of glucocerebroside in macrophages of the reticuloendothelial system Gaucher cells causes organ dysfunction and organomegaly. Gaucher cells, found in the spleen, bone marrow, lung, lymph nodes, and liver, are characteristic of the disease. There are 3 clinical types of Gaucher disease: Hepatosplenomegaly is usually present in all 3 types. Niemann-Pick disease types A and B are caused by a deficiency of sphingomyelinase which results in extensive storage of sphingomyelin and cholesterol in the liver, spleen, lungs, and, to a lesser degree, brain. Niemann-Pick type A disease is more severe than type B and characterized by early onset with feeding problems, dystrophy, persistent jaundice, development of hepatosplenomegaly, neurological deterioration, deafness, and blindness leading to death by age 3. Niemann-Pick type B disease is limited to visceral symptoms with survival into adulthood. Some patients have been described with intermediary phenotypes. Characteristic of the disease are large lipid-laden foam cells. Sphingomyelinase is encoded by the SMPD1 gene. Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase GAA; acid maltase due to mutations in the GAA gene. The estimated incidence is 1 in 40, live births. In Pompe disease, glycogen that is taken up by lysosomes during physiologic cell turnover accumulates, causing lysosomal swelling, cell damage, and, eventually, organ dysfunction. This leads to progressive muscle weakness, cardiomyopathy, and, ultimately, death. The clinical phenotype appears to be dependent on residual enzyme activity. Complete loss of enzyme activity causes onset in infancy leading to death, typically within the first year of life. Juvenile and adult-onset forms are characterized by later onset and longer survival with primary symptoms that include muscle weakness and respiratory insufficiency, though rarely, clinically significant cardiomyopathy can be seen. Since Pompe disease is considered a rare condition that progresses rapidly in infancy, the disease, when presenting as juvenile and adult-onset forms, is often diagnosed late, if at all, during the evaluation of patients presenting with muscle hypotonia, weakness, or cardiomyopathy. Treatment with enzyme replacement therapy is available and improves prognosis, making early diagnosis of Pompe disease desirable. Krabbe disease globoid cell leukodystrophy is an autosomal recessive disorder caused by a deficiency of galactocerebrosidase GALC, galactosylceramide beta-galactosidase. Galactosylceramide as with sulfated galactosylceramide is a lipid component of myelin. The absence of GALC results in globular, distended, multinucleated bodies in the basal ganglia, pontine nuclei, and cerebral white matter. There is severe demyelination throughout the brain with progressive cerebral degenerative disease affecting primarily the white matter. Severely affected individuals typically present between 3 to 6 months of age with increasing irritability and sensitivity to stimuli. Rapid neurodegeneration including white matter disease follows with death usually occurring by age 2. A subset of individuals has later onset forms of the disease that are characterized by ataxia, vision loss, weakness, and psychomotor regression. They can present anywhere from age 6 months to the seventh decade of life, and based on newborn screening experience in New York, appear to be more common than the earlier onset

variants. The clinical course of Krabbe disease can be variable, even within the same family. Of note, Krabbe disease variants, including pseudodeficiency, are not distinguishable by enzyme activity measurement. Hematopoietic stem cell transplantation, particularly when performed within the first few weeks of life, is a treatment option with potential benefit. Fabry disease is an X-linked recessive disorder with an incidence of approximately 1 in 50, males. Symptoms result from a deficiency of the enzyme alpha-galactosidase A GLA; ceramide trihexosidase. Reduced GLA activity results in accumulation of glycosphingolipids in the lysosomes of both peripheral and visceral tissues. Severity and onset of symptoms are dependent on the residual GLA activity. Symptoms can appear in childhood or adolescence and usually include acroparesthesias pain crises , multiple angiokeratomas, reduced or absent sweating, and corneal opacity. Renal insufficiency, leading to end-stage renal disease and cardiac and cerebrovascular disease, generally occurs in middle age. The variant forms of Fabry disease may be underdiagnosed. Females who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected. Enzyme replacement therapy is a treatment option for Fabry disease. Mucopolysaccharidosis I MPS I is an autosomal recessive disorder caused by a reduced or absent activity of the alpha-L-iduronidase enzyme. Deficiency of the alpha-L-iduronidase enzyme can result in a wide range of phenotypes further categorized into 3 syndromes: Clinical features and severity of symptoms of MPS I are widely variable, ranging from severe disease to an attenuated form that generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, progressive dysostosis multiplex, hepatosplenomegaly, corneal clouding, hearing loss, mental retardation or learning difficulties, and cardiac valvular disease. The incidence of MPS I is approximately 1 in , live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. Peroxisomal disorders include 2 major subgroups: Peroxisomes are organelles present in all human cells except mature erythrocytes. They carry out essential metabolic functions including beta-oxidation of very long-chain fatty acids VLCFA , alpha-oxidation of phytanic acid, and biosynthesis of plasmalogen and bile acids. These disorders are clinically diverse and range in severity from neonatal lethal to milder, later onset variants. Zellweger syndrome spectrum ZSS is a continuum of severe disorders affecting the nervous system, vision, hearing, and liver function. Most individuals present in infancy, but adult patients have been identified. The prevalence of ZSS is 1 in 50, ZSS follows autosomal recessive inheritance. Individuals with Zellweger syndrome typically die within the first year of life without making any developmental progress. Individuals with NALD or IRD typically present in childhood with developmental delays, vision loss, and hearing loss, and have a much slower disease progression. There is no specific treatment for ZSS. X-linked adrenoleukodystrophy XALD is a disorder affecting the nervous system, adrenal cortex, and testis. It is the most common of the peroxisomal disorders, affecting 1 in 17, to 1 in 21, males. A defect in the ABCD1 gene is responsible for the disease. X-ALD shows a wide range of phenotypic expressions. The clinical phenotypes occurring in males can be subdivided in 4 main categories: Treatment options are hormone replacement therapy, dietary intervention, or hematopoietic stem cell transplantation.

Chapter 4 : Peroxisomal disorder - Wikipedia

This group comprises neurological disorders that occur as the result of defects in biogenesis of peroxisomes or, directly or indirectly, in enzymes that are normally localized in peroxisomes.

Sometimes, this means that the peroxisomes themselves fail to form, or fail to form in sufficient numbers; other times "ghost peroxisomes" form, having somewhat the appearance of the real thing, but lacking the matrix enzymes necessary to function. However, there are also some distinct differences between them. Each has characteristics which set it apart from the others, and the names are not used interchangably. Because they all involve the same generalized failure, the PBDs share a common set of biochemical abnormalities: Of these, some half dozen or so seem to commonly come up as being particularly relevant to the disease states: The peroxisome is involved, along with the mitochondria, in the process of shortening these molecules to a length that either the body can use or is able to rid itself of. While not toxic in the sense of being poisonous, the accumulation of VLCFAs is disruptive to the structure and stability of the affected cells, for reasons which are not completely understood. For example, the peroxisomes are also involved in the metabolism of alcohol. It is really the complex of abnormalities that define the PBDs, and no single one should be thought of as isolated from the others. And to a large degree, there is uncertainty as to how exactly these abnormalities, or what combination of them, cause the pathology and disability of the PBDs. A child with Zellweger syndrome ZS has dysmorphic facial features with high forehead and flat nose bridge, wide-set eyes and low-set ears , and deformed limbs and joints, with calcium deposits in the cartilage. The liver and kidneys are usually diseased or abnormal. There is a fundamental malformation of the brain in the developing fetus abnormal neuronal migration , and myelination does not proceed completely hypomyelination. There is usually retinal or other eye disease, and almost always sensorineural cochlear hearing loss. The child is hypotonic and prone to epileptic seizures. There is a profound lack of any normal psychomotor development. ZS is fatal early, usually within the first year of life. There are known to be at least three different gene defects which can cause ZS: Only the specific genetic causes are different; outwardly these are all essentially the same. The dysmorphic facial features and skeletal abnormalities are less pronounced. There is no calcification of cartilage. There is liver disease, but not the kidney cysts associated with ZS. The adrenal glands are diseased. The neuronal migration defect in the developing brain is not as extensive as in ZS, but there are severe abnormalities of myelination. There is retinal or other eye disease and also sensorineural hearing loss. These children are hypotonic and prone to seizures. Psychomotor development is profoundly affected. NALD is fatal, usually within the first ten years. When it was first described, in , it took its name from these two similarities with X-linked adrenoleukodystrophy, being considered a "neonatal" form of it. This was at a time before there was even a concept, let alone systematic classification and study, of the peroxisomal disorders. A child with IRD is still very sick and has severe physical, sensory, and developmental disabilities. However, with time and patience, IRD children usually attain to some degree of motor, cognitive, and communication skills. A child with IRD has dysmorphic facial features, often of great subtlety and not recognized unless pointed out. He is apt to be small for his age, but body and limbs are correctly proportioned. The liver is typically enlarged, and there may be some amount of dysfunction. The adrenal glands are possibly affected. Myelination is abnormal, but there is no active demyelination. There is almost always retinal or other eye disease, and generally sensorineural hearing loss. In IRD, the child is usually born hearing and the loss occurs sometime between six months and a year of age. A child with IRD is probably going to be hypotonic, though not always severely. IRD is sometimes associated with seizure disorders, but not typically. Psychomotor development is severely affected, but is by no means arrested. IRD is also fatal, but survival into the teens and twenties and even beyond is known. In some cases, infants with IRD will undergo spontaneous bleeding episodes, in particular intercranial hemorrhage. This may be due to a liver dysfunction that interferes with the synthesis of vitamin K. If the child survives this, the resulting brain injury is an unknown and complicating factor in his development. Its effects, if any, can hardly be distinguished against the backdrop of the IRD. The brain injury may possibly result in a seizure disorder which otherwise would have been absent. IRD was originally called infantile

phytanic acid storage disease, the first described cases noting this specific biochemical abnormality. Since the one disease at that time known to be associated with abnormal levels of phytanic acid was Refsum disease, these cases were considered to be an "infantile" form of it. The similarities of the two were noted especially in the eye disease , but the number of differences between them were striking, and IRD and Refsum disease were always understood to be two separate entities. As with NALD, this was at a time when there was no study or classification of peroxisomal disorders. But as with NALD, the name stuck. An abnormality typical to one may show up in another, or itself be absent. It is a continuous and dynamic spectrum, from the most profoundly involved child with ZS to a teenager with IRD who bowls in Special Olympics. There is some evidence for this being the case, and it does seem a natural way of understanding it. Beyond this there is as yet no resolved picture. The actual steps from defective genes to defective peroxisomes, from abnormal biochemistry to the disease states, are not fully understood. Hyperpipecolic acidemia [MIM No. The described cases are thought to be indistinguishable from either NALD or IRD, and the term hyperpipecolic acidemia was eventually considered unnecessary. There is at least one described case referred to as pseudo-IRD. This was considered to be a PBD, as catalase-containing peroxisomes did not exist. There were, however, peroxisome-like structures which did contain some peroxisomal matrix proteins, and in which some processes did continue almost normally. The peroxisome biogenesis disorders are autosomal recessive. They occur in all countries and among all races and ethnic groups. They are diseases of extreme rarity, but any discussion of just how rare immediately falters. Estimates of birth frequencies vary from 1: Consistent and reliable census data is itself the rarity. There is no cure. In general, what therapies do exist are dietary: The theory here is that the pathology and disabilities of these diseases are caused by the biochemical abnormalities even without always understanding just how and that therefore they can possibly be alleviated by artificially correcting those abnormalities. This is a reasonable line of thought, and dietary therapies of various kinds are widely practiced. Nor would there be any medical consensus on what that diet should be anyway. Commonly, seizure disorders are treated with anti-convulsants, and IRD children with the bleeding disorder take vitamin K to control it. Peroxisomal Multi-Enzyme Disorders These are diseases in which several of the proteins necessary to peroxisomal function are lacking, but there is not a global loss of function as in the PBDs. Because it contains catalase, the peroxisome itself is considered intact, and not the result of a general assembly failure. However, this classification is not universally used and sometimes these diseases are counted among the PBDs i. Considered this way, the peroxisome biogenesis disorders fall into four groups and include RCDP: These dysfunctions result in the impaired synthesis of ether-phospholipids, the malformation of an enzyme necessary to liver function, and the impaired oxidation with subsequent accumulation of phytanic acid. RCDP is recognized by this particular set of abnormalities. Chondrodysplasia punctata is a broader term, including other disorders which are not peroxisomal, or not definitely determined to be e. RCDP is the most severe of these; the term is reserved for the peroxisomal disorder. RCDP is characterized by certain skeletal abnormalities from which it derives its name, a dwarfism marked by a disproportionate shortening of the upper limbs rhizomelia , and abnormalities in the formation of cartilage chondrodysplasia punctata, specifically an abnormal calcification of cartilage. Her psychomotor development is severely affected. At its most severe, RCDP is fatal within the first year; however survival into the teens is known. To somewhat complicate the nomenclature there are also several described cases in which RCDP is not associated with rhizomelia. This non-rhizomelic yet peroxisomal CDP is genetically and biochemically identical to RCDP, and is understood to be a less severe form of it, not a separate disorder. Zellweger-like syndrome is known by only one possibly two described case s , both fatal in infancy. As is evident from the name, it was similar in appearance to ZS, but was determined to be a defect of three particular enzymes and not a general loss of peroxisome function. Peroxisomal Single-Enzyme Disorders These are disorders in which the peroxisome is intact and functioning, except that there is a defect in just one enzymatic process, resulting in just one primary biochemical abnormality. The identification of the single-enzyme disorders is ongoing. With the exception of X-ALD, all of these disorders are autosomal recessive.

Chapter 5 : PLSD - Clinical: Lysosomal and Peroxisomal Storage Disorders Screen, Blood Spot

The Peroxisomal Diseases Section of the Genetics Laboratories assays blood, urine, fibroblasts and cultured CVS/amniocytes for fatty acid abnormalities associated with diseases such as: Adrenoleukodystrophy.

Blood cells transport nutrients throughout the body and fight viruses and infections. Kidney cells remove waste from the body so that it can be excreted through the effort of the cells in the bladder. The list could go on and on. Even though each cell has a specific function in the human body, every kind of cell has virtually the same structure consisting of a cytoplasm enclosed by a membrane within which are the nucleus and various organelles. One important organelle is the peroxisome, which is found in nearly every complex or eukaryotic cell. Peroxisomes are organelles that help the cell metabolize certain chemicals and deal with the waste the cell produces. They are called peroxisomes because they work to convert certain substances into peroxide and then to convert peroxide into water. They are very important to cell function because while it is needed to metabolize certain chemicals and keep the cell functioning, peroxide is also toxic and there must be a way to rid it from the body. Without peroxisomes there could be no way to produce the peroxide necessary for metabolism, nor could there be any way to get rid of it from the body. Peroxisomes â€" some basic information on the cell structures called peroxisomes Cells Alive â€" interactive model of the human cell with information on peroxisomes Peroxisomes and Nuclei â€" some basic information on cell organelles including peroxisomes and nuclei Normal Function of Peroxisomes For such a small organelle, peroxisomes really perform some complex functions. First, there are enzymes in each peroxisome that take oxygen and then use it to remove hydrogen from certain molecules that have entered the cell. In the process, hydrogen peroxide is produced. Other enzymes in the peroxisome then use the hydrogen peroxide for oxidizing other molecules like alcohol, phenols, and more. This reaction ends up converting the hydrogen peroxide into water, which is not toxic. The kidneys and livers make extensive use of these processes to eliminate waste from the blood stream. Peroxisomes also work to break fatty acids down into their constituent carbon atoms, and they are important for producing certain proteins in the body as well. Peroxisomes â€" information on peroxisomes from the Florida State University Peroxisomes and Cell Function â€" complete overview of peroxisomes and their functions in living cells from the NIH Peroxisome Database â€" extensive information on all things related to peroxisomes Diseases Related to Peroxisomes Peroxisome disorders are linked to several diseases in the human body, many of which appear during childhood and are fatal. Persons who have this disease lack a protein that helps transport fatty acids into the peroxisomes. These fatty acids cannot break down and build up in the body, eventually damaging the brain and nervous system. A second well-known peroxisomal disease is called Zellweger Syndrome. Persons with this syndrome lack peroxisomes entirely or have a greatly reduced number of them. Fatty acids cannot be broken down on account of this, leading to brain damage and death. There is no cure for Zellweger, and those who have it do not usually live past six months of age. Peroxisomal Disorders â€" page on peroxisomal diseases from the famous drug company Peroxisomal Disorders â€" a page all about the disorders and diseases related to peroxisomes Ians Story: Peroxisomal Disorders â€" parents of a child with a peroxisomal disease developed this page to educate people about said diseases Zellweger Syndrome â€" information on one of the more well known peroxisomal diseases Peroxisomes may be small, but they are very important. Having a better understanding of them helps us appreciate the complexity of the human body and the problems that arise when they do not function properly.

Chapter 6 : Peroxisomes and Disease - An Overview

Peroxisomal disorders are a large group of genetic disorders (some can also be considered "inborn errors of metabolism"). These conditions vary in symptoms and age of onset. However, they share a problem with the functioning of the peroxisome.

As their name indicates, they use molecular oxygen in oxidative reactions that generate hydrogen peroxide. They also contain catalase peroxidase , which uses H2O2 to oxidize other substrates. This reaction is especially important in detoxifying ethanol, formic acid, and other toxins. Peroxisomes can be identified by light microscopy by their catalase activity using the diaminobenzidine reaction. Peroxisomal enzymes catalyze several anabolic and catabolic reactions. The most important of these are plasmalogen synthesis and very long chain fatty acid VLCFA beta oxidation. Plasmalogens are the most abundant phospholipids in myelin. The products of VLCFA beta oxidation are used for biosynthesis of cholesterol, bile acids, and other compounds. The peroxisome has a single membrane which encloses the peroxisomal matrix. The peroxisomal membrane is a lipid bilayer with embedded peroxisomal membrane proteins. All peroxisomal membrane proteins and enzymes of the peroxisomal matrix are encoded by nuclear genes, synthesized on free ribosomes, and imported into the peroxisomes. The proteins that are involved in peroxisomal biogenesis are called peroxins and are encoded by PEX genes. Fifteen human PEX genes are known. There are two types of peroxisomal disorders: The former are caused by mutations of genes encoding specific peroxisomal enzymes. PBDs are caused by mutations of PEX genes that are involved in the biogenesis and function of peroxisomes and are characterized by deficiencies of multiple peroxisomal enzymes and, in some cases, by absence or reduction in the number of peroxisomes. The most severe and important PBD is the Zellweger spectrum. The incidence of peroxisomal disorders is 1: Most peroxisomal disorders cause severe neurological dysfunction due to CNS malformations migration defects , myelin abnormalities, and neuronal degeneration. Non-neurological manifestations include dysmorphic features, liver dysfunction and skeletal abnormalities. The key biochemical abnormalities of peroxisomal disorders and the basis for their laboratory diagnosis are elevation of VLCFAs and decreased RBC plasmalogens. All peroxisomal disorders except X-linked adrenoleukodystrophy are autosomal recessive. As in other genetic disorders, several mutations of each gene are seen, some of them severe and others milder. Mutations of different genes can cause similar phenotypes. The unique biogenesis of peroxisomes and multiple interactions of PEX genes explain the genetic and phenotypic complexity of peroxisomal disorders. It is now clear that they represent a phenotypic spectrum, the ZSD, which is caused by mutations of 12 PEX genes resulting in abnormal peroxisomal biogenesis. The clinical findings of the ZS are dysmorphic features prominent forehead, hypertelorism, epicanthal folds, flat supraorbital ridges, broad nasal bridge, large fontanelles , neurological abnormalities hypotonia, decreased sucking, decreased tendon reflexes, seizures, nystagmus, contractures , liver disease, and calcific stippling of the patellae. Most ZS patients have failure to thrive and die by six months of age. The general pathological changes in the ZS are cholestasis, hepatic fibrosis, and cortical renal cysts. Hepatocellular peroxisomes are absent or severely decreased. Adrenocortical cells and macrophages contain diverse lipid materials including characteristic trilamellar inclusions. The brain, in the ZS, shows neuronal migration defects NMDs , white matter abnormalities, and lipid storage. Cirrhosis Cirrhosis in the Zellweger syndrome ZS. Pachygyria Pachygyria in the Zellweger syndrome. Lipid products in the cerebellum. The most severe NMD is perisylvian pachygyria with polymicrogyria in the adjacent frontoparietal areas. The topography and cytoarchitecture of this lesion are characteristic of the ZS. The cerebellum shows microgyria and heterotopic islands of Purkinje and granular cells in the white matter. The neuronal ribbons of the dentate nuclei and inferior olives lose their elaborate folding or are discontinuous. The abnormality of neuronal migration may be due to impairment of cellular interactions and signaling due to incorporation of abnormal fatty acids into neuronal membranes. The white matter in the ZS is reduced in mass and shows deficient myelin. Sudanophilic lipid products accumulate throughout the brain in macrophages, neurons, and glial cells. These macrophages contain a variety of abnormal lipid products including trilamellar inclusions. NALD has similar but milder dysmorphic features

and neurological abnormalities to the ZS, and patients survive on average for three years and some of them into adolescence. Hepatic fibrosis and cirrhosis are common, and hepatocellular peroxisomes are normal or reduced. The brain shows polymicrogyria, subcortical heterotopias, and cerebellar dysplasia, but no pachygyria. Infantile Refsum disease infantile phytanic acid storage disease. IRD is characterized by psychomotor retardation, sensorineural deafness, pigmentary degeneration of the retina, anosmia, and minor dysmorphic features. Patients survive into adolescence or adulthood. The liver is enlarged and cirrhotic and hepatocytes contain lamellar inclusions similar to phytol inclusions seen in chloroplasts of plant cells. The adrenals are atrophic and the adrenal cortex contains ballooned and striated cells. MRI studies show diffuse white matter atrophy. Biochemical studies show elevation of phytanic acid, hence the term infantile phytanic acid storage Refsum disease. Peroxisomes are absent or reduced. VLCFA accumulation in the adrenal cortex causes adrenal atrophy. Adrenal insufficiency begins early in childhood. Neurological manifestations appear a few years later, usually between age five and ten. The initial abnormalities are apathy and behavioral change. Visual loss, spasticity, and ataxia follow, and patients usually die a few years after the onset of neurologic symptoms. A variant of X-ALD, adrenomyeloneuropathy AMN , is characterized by adrenal insufficiency since childhood with progressive spastic paraparesis, peripheral neuropathy, cerebellar ataxia, and intellectual deterioration beginning in the third decade. Neuropathologically, X-ALD is characterized by diffuse myelin loss, lipid-laden histiocytes, and perivascular lymphocytic infiltrates,especially in areas of active myelin breakdown. Myelin loss is especially prominent in the right hemisphere. Lipid macrophages, lymphocytes, and reactive astrocytes in the white matter. Thus, myelin loss in X-ALD is probably due to two causes, chemical imbalance and inflammation. Advanced cases show white matter atrophy and gliosis. Characteristic cellular inclusions trilamellar membranes containing VLCFA cholesterol esters are seen with the electron microscope in adrenal cortical cells, white matter histiocytes, Leydig cells, and Schwann cells. Nat Clin Pract Neurol.

Chapter 7 : Peroxisomal Disorders - Child Neurology Foundation

Peroxisomal disorders are a group of congenital (existing from birth) diseases characterized by the absence of normal peroxisomes in the cells of the body. Peroxisomes are special parts (organelles) within a cell that contain enzymes responsible for critical cellular processes, including oxidation.

What is a peroxisomal disorder? Peroxisomal disorders are rare, genetic, terminal conditions that affect all major organ systems of the body. Peroxisomes are necessary for cell function, normal brain development, and the formation of myelin. Why do peroxisomal disorders have so many different names? As the understanding of this disorder has grown, there has been a movement away from the original disease categories towards a continuum of disease severity for PBD-ZSD, ranging from most severe Zellweger syndrome , intermediate neonatal adrenoleukodystrophy , and mild infantile Refsum disease and Heimler syndrome. Some hallmark symptoms that children with PBD-ZSD commonly experience are hearing and vision loss, hypotonia, neurological issues, seizures, developmental delay, feeding issues, adrenal insufficiency, leukodystrophy, and liver, kidney, and bone disease. Most children with PBD-ZSD will show some form of craniofacial differences such as a high forehead, broad nasal bridge, low set ears, epicanthal folds, or a large fontanel. Early symptoms in newborns may be profound low muscle tone, seizures, apnea, hearing and vision difficulties, and an inability to eat. What causes peroxisomal disorders? PBD-ZSD is an autosomal recessive disorder, meaning that both the mother and father of a patient have to carry the recessive gene for it. Most commonly, patients have mutations in one of 13 PEX genes required for normal organelle assembly. This mutation causes one of two major types of peroxisomal disorders: How are peroxisomal disorders diagnosed? Although it is estimated that 1 in 50, births are affected by PBD-ZSD, actual diagnoses may increase as newborn screening for peroxisomal disorders is introduced across the U. A team of specialists to help treat symptoms may include a pediatrician, endocrinologist, neurologist, physical therapist, speech therapist, special education teacher, opthamologist and audiologist. There are current clinical trials in place to better understand these disorders in the hope that future treatments for the many symptoms of PBD-ZSD become available. Because PBD-ZSD is a spectrum disorder, there is a wide range of life expectancy for patients with peroxisomal disorders. Our Scientific Advisory Board includes the foremost researchers and physicians in the field of peroxisomal disorders. In their roles as advisers, members collaborate with each other and with our Board of Directors and staff in order to better guide and support our families and the research initiatives of the GFPD. Our Mission The mission of the GFPD is to fund and promote peroxisome disorder research and to assist families and professionals through educational programs and support services related to Zellweger spectrum disorders.

Chapter 8 : Peroxisomes and Related Diseases

Transmission Most peroxisomal disorders are inherited autosomal recessive diseases. This means that both parents need to be carriers of the defective gene in order for a child to develop the disease.

Description Peroxisomes are organelles within a cell that contain enzymes responsible for critical cellular processes. A cell can contain several hundred peroxisomes, round or oval bodies with diameters of about 0. By definition, a peroxisome must contain catalase, which is an enzyme that breaks down hydrogen peroxide. Peroxisomal disorders are subdivided into two major categories: There are about 25 known peroxisomal disorders, although the number of diseases that are considered to be separate, distinct peroxisomal disorders varies among researchers and healthcare practitioners. Approximately 50 different biochemical reactions occur entirely or partially within a peroxisome. Some of the processes are anabolic constructive , resulting in the synthesis of essential biochemical compounds, including bile acids, cholesterol, plasmalogens, and docosahexanoic acid DHA , which is a long chain fatty acid that is a component of complex lipids, including the membranes of the central nervous system. Other reactions are catabolic destructive and lead to the destruction of some fatty acids, including very long chain fatty acids VLCFAs, fatty acids with more than 22 carbon atoms in their chains , phytanic acid, pipecolic acid, and the prostoglandins. When VLCFAs accumulate due to abnormal functioning of the peroxisomes, they are disruptive to the structure and stability of certain cells, especially those associated with the central nervous system and the myelin sheath , which is the fatty covering of nerve fibers. The peroxisomal disorders that include effects on the growth of the myelin sheath are considered to be part of a group of genetic disorders referred to as leukodystrophies. Peroxisomal disorders form a heterogeneous disease group, with different degrees of severity. The differences among these disorders are continuous, with overlap between abnormalities. Examples of peroxisomal disorders are: X-linked adrenoleukodystrophy X-ALD , a sex-linked disorder characterized by progressive symptoms that begin as behavioral changes, muscle weakness, and speech difficulties. Zellweger syndrome ZS , which is usually fatal within the first year of life. Neonatal adrenoleukodystrophy NALD , which is usually fatal within the first ten years. Infantile Refsum disease IRD , which is not as devastating as ZS and NALD, as the children with this disorder with time and patience can develop some degree of motor, cognitive, and communication skills , although death generally occurs during the second decade of life. Rhizomelic chondrodysplasia punctata RCDP , which in its most severe form is fatal within the first year or two of life; however, survival into the teens has been known to occur. It is characterized by shortening of the proximal limbs i. Zellweger-like syndrome, which is fatal in infancy and known to be a defect of three particular enzymes. Transmission Most peroxisomal disorders are inherited autosomal recessive diseases. This means that both parents need to be carriers of the defective gene in order for a child to develop the disease. If both parents are carriers but do not show signs of disease, each child has a 25 percent chance of having the disease. If one parent has the disease and the other is a carrier, each child has a 50 percent chance of having the disease. As a sex-linked genetic disorder, the daughters of males affected with X-ALD become carriers and the sons are not affected. The children of female carriers have a 50 percent chance of having the genetic mutation, which means that sons who inherit the mutation have the disease, and daughters who inherit the mutation are carriers. Demographics Peroxisomal disorders occur in all countries, among all races and ethnic groups. They are extremely rare, with frequencies reported at one in 30, to one in ,, although these numbers are only estimates. X-ALD is the most common of the peroxisomal disorders, affecting about one in 20, males. It is estimated that there are about 1, people in the United States with the disorder. ZS is estimated to affect one in 50, to , live births. Causes and symptoms The range of disease abnormalities may be a result of a corresponding range of peroxisome failure. For example, in severe cases of ZS, the failure is nearly complete, while in IRD, there is some degree of peroxisome activity. In peroxisomal single-enzyme disorders, the peroxisome is intact and functioning, but there is a defect in only one enzymatic process, with only one corresponding biochemical abnormality. These disorders, however, can be as severe as those in which peroxisomal activity is nearly or completely absent. In general, developmental delay , mental retardation , and vision and hearing impairment

are common in those who have these disorders. Acquisition of speech appears to be especially difficult, and because of the reduced communication abilities, autism is common in those who live longer. Peroxisomal disorder patients have decreased muscle tone hypotonia , which in the most severe cases is generalized, while in less severe cases, is usually restricted to the neck and trunk muscles. Sometimes this lack of control is only noticeable by a curved back in the sitting position. Head control and independent sitting is delayed, with most patients unable to walk independently. Failure to thrive is a common characteristic of patients with peroxisomal disorder, along with an enlarged liver, abnormalities in liver enzyme function, and loss of fats in stools steatorrhea. Peroxisomal disorders are also associated with facial abnormalities, including high forehead, frontal bossing swelling , small face, low set ears, and slanted eyes. These characteristics may not be prominent in some children and are especially difficult to identify in an infant. Onset of X-ALD-related neurological symptoms occurs at about five to 12 years of age, with death occurring within one to ten years after onset of symptoms. In addition to physical abnormalities seen in other types of peroxisomal disorders, common symptoms of X-ALD also include behavioral changes such as abnormal withdrawal or aggression, poor memory, dementia, and poor academic performance. Other symptoms are muscle weakness and difficulties with hearing, speech, and vision. As the disease progresses, muscle tone deteriorates, swallowing becomes difficult, and the patient becomes comatose. There are also milder forms of X-ALD, an adult onset ALD that typically begins between the ages of 21 and 35, and a form that is occasionally seen in women who are carriers of the disorder. In addition to X-ALD, there are at least ten other single-enzyme peroxisomal disorders, each with its own specific abnormalities. When to call the doctor A healthcare provider should be contacted if a child develops symptoms suggestive of peroxisomal disorder or if a child already diagnosed with a peroxisomal disorder shows signs of worsening disease. Diagnosis Since hearing and vision deficiencies may be difficult to identify in infants, peroxisomal disorders are usually detected by observations of failure to thrive, hypotonia, mental retardation , widely open fontanel, abnormalities in liver enzymes, and an enlarged liver. If peroxisomal disorders are suspected, blood plasma assays for VLCFAs, phytanic acid, and pipecolic acid are conducted. Additional tests include plasmalogen biosynthesis potential. It is possible to diagnose peroxisomal disorders in utero. For example, for X-ALD, diagnosis can be made from cultured skin fibroblasts or amniotic fluid cells. This allows prenatal diagnosis and carrier identification in 90 percent of those affected. As of the early s it has been shown that biochemical diagnosis can be performed through chorionic villus testing, a procedure performed very early in the first trimester of pregnancy. Treatment For many of the peroxisomal disorders, there is no standard course of treatment, with supportive treatment strategies focusing on alleviation of complications and symptoms. Bone marrow transplants may be effective for children with X-ALD if administered early in the course of the childhood form of the disease. Physical and psychological therapies are important for all types of peroxisomal disorders. Alternative treatment Patients with peroxisomal disorders, and particularly X-ALD, have been treated with a mixture of glycerol trioleate-glycerol trieucate 4: Other diets that have been tried with varying success include dietary supplementation with plasmalogen precursors to increase plasmalogen levels and with cholic acid to normalize bile acids. Nutritional concerns In general, most treatments that are attempted for peroxisomal disorders are dietary, whereby attempts are made to artificially correct biochemical abnormalities associated with the disorders. Therapies include supplementation of the diet with antioxidant vitamins or limitation of intake of fatty acids, especially VLCFAs. Another area of dietary therapy that is being investigated is the supplementation of the diet with pure DHA, given as early in life as possible, in conjunction with a normal well-balanced diet. Some results have indicated that if given soon enough during development, DHA therapy may prevent some of the devastating consequences of peroxisomal disorders, including the loss of vision and brain damage. Other treatment strategies include addition of important missing chemicals. For example, in disorders where there is faulty adrenal function, replacement adrenal hormone therapy is used. Any dietary changes should be monitored biochemically to determine if the supplements are having their desired effects and are not causing additional adverse effects. Prognosis Peroxisomal disorders range from life-threatening to cases in which people may function with some degree of mental and motor delays. As of , there was not yet a cure for peroxisomal disorders. Enzyme replacement therapies, including enzyme infusion, transplantation,

and gene therapy , may hold promise for future advances in the treatment of these disorders. As of the early s research is conducted in order to increase scientific understanding of these disorders and find ways to prevent, treat, and cure them. Prevention It is not possible to prevent the transmission of an abnormal peroxisomal gene from parent to child or spontaneous mutations that may arise. Parental concerns Numerous professional and parent-led organizations exist to support parents as they first learn of a peroxisomal disorder diagnosis and as they provide care for their child. Genetic counseling is recommended for known or suspected carriers. As genes are identified that result in the disorders, genetic testing is being developed to identify carriers, who then can manage their reproduction to avoid the possibility of children being born with these deficiencies. The outer tissue of the glands cortex produces several steroid hormones, while the inner tissue medulla produces the hormones epinephrine adrenaline and norepinephrine. Autosomal recessive mutation â€”A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease. Autosome â€”A chromosome not involved in sex determination. Enzyme â€”A protein that catalyzes a biochemical reaction without changing its own structure or function. Fontanelle â€—One of several "soft spots" on the skull where the developing bones of the skull have yet to fuse. Organelle â€—A specialized structure within a cell, which is separated from the rest of the cell by a membrane composed of lipids and proteins, where chemical and metabolic functions take place. Edited by Richard E Behrman et al.

Chapter 9 : Peroxisomal Disorders

Paker AM, Sunness JS, Brereton NH, et al. Docosahexaenoic acid therapy in peroxisomal diseases: results of a double-blind, randomized trial. Neurology ; Wei H, Kemp S, McGuinness MC, et al. Pharmacological induction of peroxisomes in peroxisome biogenesis disorders.

Peroxisomal disorders Definition Peroxisomal disorders are a group of congenital diseases characterized by the absence of normal peroxisomes in the cells of the body. Description Peroxisomes are organelles within a cell that contain enzymes responsible for critical cellular processes. A cell can contain several hundred peroxisomes, round or oval bodies with diameters of about 0. By definition, a peroxisome must contain catalase, which is an enzyme that breaks down hydrogen peroxide. Peroxisomal disorders are subdivided into two major categories: There are about 25 known peroxisomal disorders, although the number of diseases that are considered to be separate, distinct peroxisomal disorders varies among researchers and healthcare practitioners. Approximately 50 different biochemical reactions occur entirely or partially within a peroxisome. Some of the processes are anabolic constructive , resulting in the synthesis of essential biochemical compounds, including bile acids, cholesterol, plasmalogens, and docosahexanoic acid DHA , which is a long chain fatty acid that is a component of complex lipids, including the membranes of the central nervous system. Other reactions are catabolic destructive and lead to the destruction of some fatty acids, including very long chain fatty acids VLCFAs, fatty acids with more than 22 carbon atoms in their chains , phytanic acid, pipecolic acid, and the prostoglandins. When VLCFAs accumulate due to abnormal functioning of the peroxisomes, they are disruptive to the structure and stability of certain cells, especially those associated with the central nervous system and the myelin sheath, which is the fatty covering of nerve fibers. The peroxisomal disorders that include effects on the growth of the myelin sheath are considered to be part of a group of genetic disorders referred to as leukodystrophies. Peroxisomal disorders form a heterogeneous disease group, with different degrees of severity. The differences among these disorders are continuous, with overlap between abnormalities. Examples of peroxisomal disorders are: X-linked adrenoleukodystrophy X-ALD , a sex-linked disorder characterized by progressive symptoms that begin as behavioral changes, muscle weakness, and speech difficulties. Zellweger syndrome ZS , which is usually fatal within the first year of life. Neonatal adrenoleukodystrophy NALD , which is usually fatal within the first ten years. Infantile Refsum disease IRD , which is not as devastating as ZS and NALD, as the children with this disorder with time and patience can develop some degree of motor, cognitive, and communication skills , although death generally occurs during the second decade of life. Rhizomelic chondrodysplasia punctata RCDP , which in its most severe form is fatal within the first year or two of life; however, survival into the teens has been known to occur. It is characterized by shortening of the proximal limbs i. Zellweger-like syndrome, which is fatal in infancy and known to be a defect of three particular enzymes. Transmission Most peroxisomal disorders are inherited autosomal recessive diseases. This means that both parents need to be carriers of the defective gene in order for a child to develop the disease. If both parents are carriers but do not show signs of disease, each child has a 25 percent chance of having the disease. If one parent has the disease and the other is a carrier, each child has a 50 percent chance of having the disease. As a sex-linked genetic disorder, the daughters of males affected with X-ALD become carriers and the sons are not affected. The children of female carriers have a 50 percent chance of having the genetic mutation, which means that sons who inherit the mutation have the disease, and daughters who inherit the mutation are carriers. Demographics Peroxisomal disorders occur in all countries, among all races and ethnic groups. They are extremely rare, with frequencies reported at one in 30, to one in ,, although these numbers are only estimates. X-ALD is the most common of the peroxisomal disorders, affecting about one in 20, males. It is estimated that there are about 1, people in the United States with the disorder. ZS is estimated to affect one in 50, to , live births. Causes and symptoms The range of disease abnormalities may be a result of a corresponding range of peroxisome failure. For example, in severe cases of ZS, the failure is nearly complete, while in IRD, there is some degree of peroxisome activity. In peroxisomal single-enzyme disorders, the peroxisome is intact and functioning, but there is a defect in only

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