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Fatty Acid Alpha-oxidation and its Clinical Correlation

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Abstract:
The human diet includes branched chain fatty acid phytanic acid (3,7,11,15-tetramethylhexadecanoic acid) and the degradation of 2-hydroxyphytanoyl-CoA, the initial step in the oxidation of phytanic acid was investigated. But, the long-standing controversy about the mechanism and subcellular location of phytanic acid alpha-oxidation has been debated and remain incompletely understood. Phytanic acid is known to undergo one cycle of alpha-oxidation initially due to its methyl group at the beta-position. The metabolic pathway known as Alpha oxidation of fatty acid is important for the production of energy, the elimination of toxic metabolites, the metabolism of lipids, the regulation of fatty acid levels, and developmental processes. The resulting pristanic acid can undergo further oxidation through a peroxisomal process called beta oxidation.

Throughout the years, even more diseases including the accumulation of phytanic acid along with other metabolites were documented. Numerous hereditary disorders that affect mitochondrial fatty acid beta-oxidation, peroxisomal fatty acid beta-oxidation, or mitochondrial fatty acid alpha-oxidation have been found in humans. Defective alpha-oxidation in peroxisome biogenesis disorders causes phytanic acid levels to accumulate, resulting in Refsum disease, a rare autosomal recessive disorder. Only a few, unfavorable alternatives to treatment are available. The prognosis for Refsum disease is still not promising. Consequently, this brief review is to summarize the biochemistry of alpha fatty acid oxidation, the effects of the biochemical defect and its associated disease, and the clinical hallmarks of Refsum disease, which have been associated to the degradation of exogenous 3-methyl-branched fatty acid.

Keywords:
Alpha oxidation, Cardiac arrhythmias, Cerebellar ataxia, Phytanic acid, Plasmapheresis, Refsum disease, Retinitis Pigmentosa

INTRODUCTION

The human body has several subcellular locations where fatty acid oxidation takes place: the mitochondria, where only beta-oxidation occurs; the peroxisome, where both alpha- and beta-oxidation take place; and the endoplasmic reticulum, where omega-oxidation occurs. The metabolic pathway known as alpha oxidation of fatty acids takes place in the peroxisome and is responsible for breaking down by-products of chlorophyll, which is found in green vegetables and fruits [1]. Phytanate, also known as phytanic acid, is a branched chain saturated fatty acid with four methyl groups, one of which is at the C-3 position, and a C16 backbone. It is the most widely studied substrate the primary molecule that requires the enzymes committed to alpha-oxidation [2]. Additionally, extra enzymatic modification is required for branched-chain fatty acids to enter the peroxisomes' alpha-oxidation pathway [1]. Humans do not synthesize phytanic acid; instead, it is derived from food. Phytol is the breakdown product of chlorophyll that is used to make phytanate. Marine organisms and ruminants both contain phytanate, which is produced by rumen bacteria. Phytol can also be metabolized by humans to produce phytanoyl-CoA, when phytanate from food is consumed. [2,3]. A human peroxisomal fatty acid α-oxidation pathway for β-methyl branched (3-methyl branched) long chain fatty acids consists a methyl group at C-3 hinders the third step of β-oxidation. It is first eliminated by α-oxidation, allowing the fatty acid to start β-oxidation. Peroxisomal α-oxidation of 2-hydroxylated straight chain (unbranched) fatty acids can occur in addition to the α-oxidation of β-methyl branched fatty acids. These long-chain or very long-chain fatty acids with even numbers undergo oxidation and turn into odd chain. These 2-hydroxy fatty acids are often found as the N-acyl chain of ceramide in a subgroup of mammalian sphingolipids [4]. It was discovered that this C-2 hydroxylation is catalyzed by a fatty acid 2-hydroxylase that is encoded by the gene FA2H [5-10]. A deficiency of peroxisomes, or key peroxisomal metabolic pathways can give rise to several disorders including Refsum disease. This disease can be caused by mutations in gene PHYH. Such mutations result in elevated phytanate levels that have pathological consequences [2,11] and *can* be life threatening if undiagnosed. Therefore, this review briefly presents the biochemistry of fatty acid alpha oxidation and clinical manifestations associated with the defect in alpha oxidation.

Dietary phytanic acid in human

The first report of phytanic acid in humans was made in 1963 by Klenk and Kahlke [12], who discovered phytanic acid in lipid fractions of a patient's liver, kidney, and brain suspected to suffer from Refsum Syndrome [13]. Phytol, the isoprenoid side chain of chlorophyll, is the source of phytanic acid. As chlorophyll-bound phytol cannot be metabolized by humans, and free phytol is present only in negligible amounts in food, the phytanic acid present in the human body is frequently provided by external sources [14]. Phytanic acid consumption in humans ranges from 50 to 100 mg on average per day, although dietary composition has a significant impact on this quantity. Dairy products like butter and cheese, as well as ruminant fats found in meat products, contain relatively high concentrations of phytanic acid. Based on the ruminants' diet, these levels might change significantly. Humans and other mammals (mice, rats) may readily absorb phytanic acid, which degrades rapidly [15].

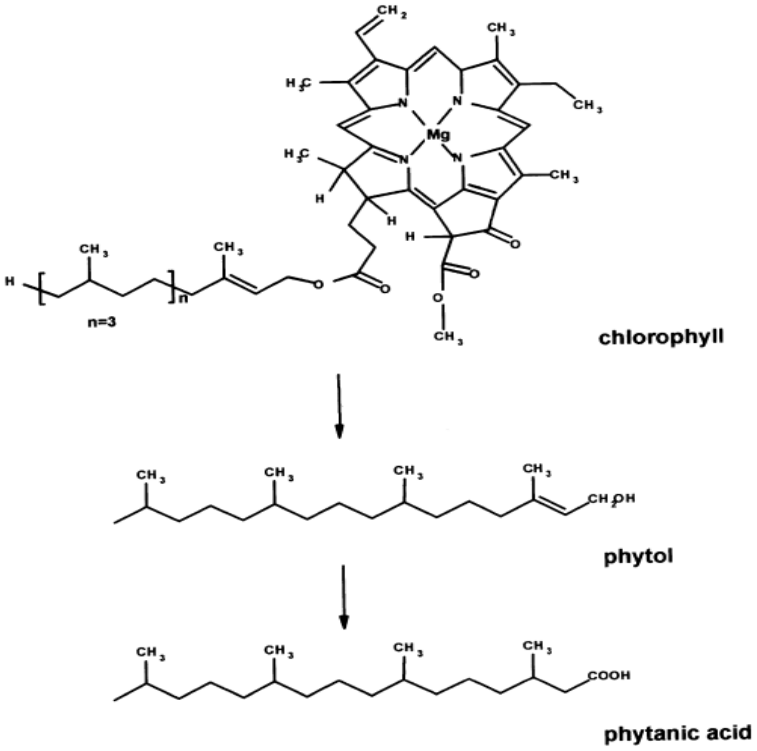


Figure 1| Chemical structures of chlorophyll, phytol and phytanic acid (3,7,11,15-tetramethylhexadecanoic acid) [14]

Fatty acid alpha oxidation

Alpha oxidation (α-oxidation) is a process by which certain branched-chain fatty acids are broken down by removal of a single carbon from the carboxyl end [16]. For 3 methyl branched fatty acids, this is the preferred pathway as their breakdown by beta-oxidation is impossible. Indeed, the 3-methyl-branch precludes the third step of b-oxidation, the dehydrogenation step. Phytanic acid, also known as 3,7,11,14-tetramethylhexadecanoic acid is at present the only established physiological substrate of a-oxidation in humans that requires additional peroxisomal enzymes to undergo beta-oxidation [17].

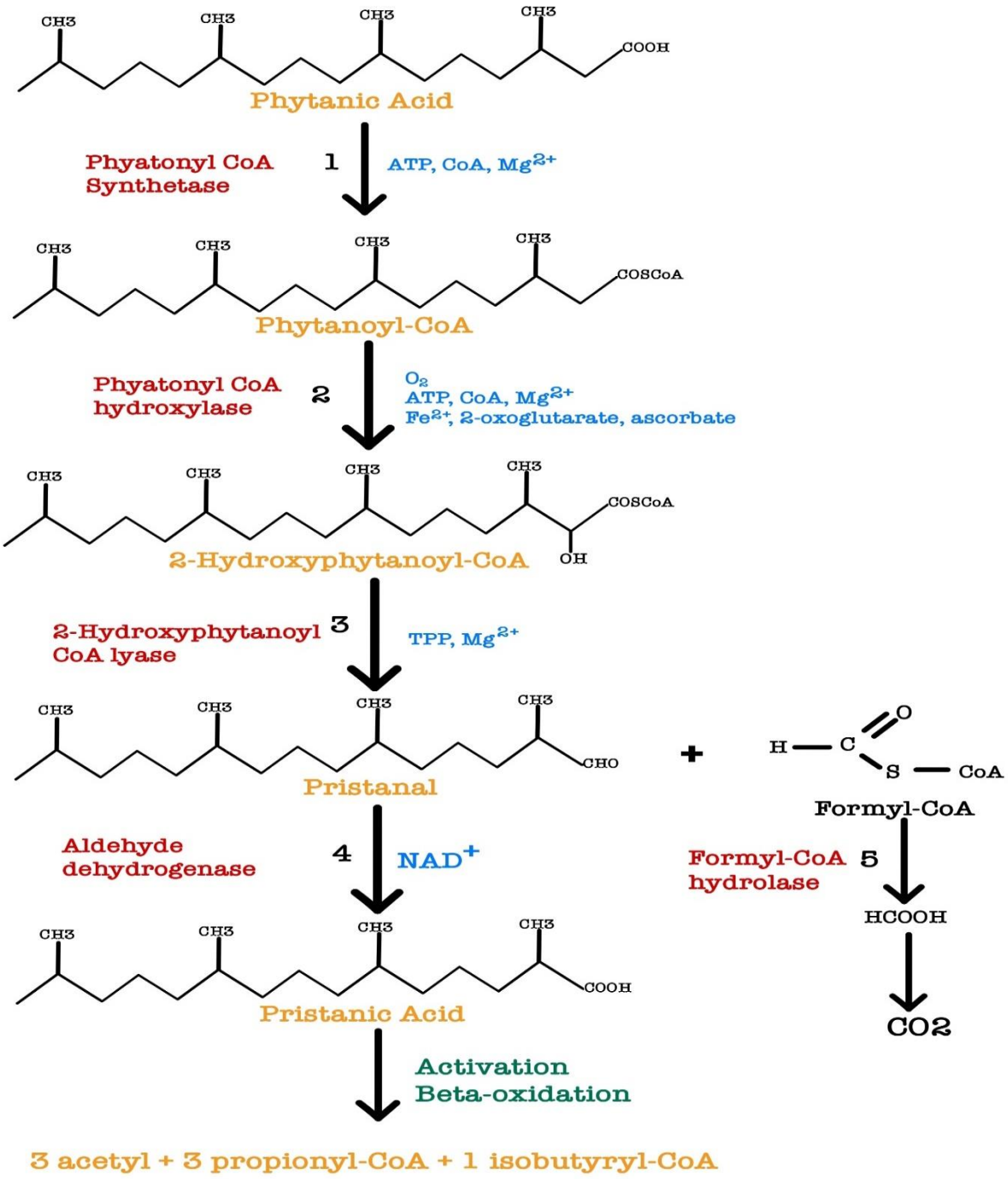


Figure 2| α-Oxidation of 3-methyl-branched fatty acids. The scheme represents the α-oxidation pathway of phytanic acid. The numbers indicate the enzymes catalysing the different steps: (1) Phyatonyl CoA synthetase; (2) phytanoyl-CoA hydroxylase (PAHX); (3) 2-hydroxyphytanoyl-CoA lyase (2-HPCL); (4) and aldehyde dehydrogenase; (5) formyl-CoA hydrolase [14]

Initially, phytanic acid activates to phytanyl CoA. The PHYH gene-encoded phytanyl CoA hydroxylase, or alpha-hydroxylase, subsequently adds a hydroxyl group to the alpha carbon. After that, the alpha carbon-hydroxyl bond undergoes two successive rounds of oxidation to form pristanic acid. Pristanic acid undergoes beta-oxidation, which produces acetyl CoA and propionyl CoA in alternative rounds. This process typically terminates when the carbon chain length reaches 6–8 carbons, similar to peroxisomal beta-oxidation of very long chain fatty acids (VLCFAs). At that point, the molecule is transported to the mitochondria by carnitine for complete oxidation to carbon dioxide and water [18]. The availability of oxygen, the concentration of fatty acids, and the activity of the enzymes involved in the pathway are the factors that regulates the rate of alpha oxidation of fatty acids [19].

Steps of alpha Oxidation

Fatty acid degradation is finally the result of a sequence of enzyme events known as the alpha oxidation pathway. The end outcome is the generation of acetyl-CoA, which can be used in the citric acid cycle or other metabolic pathways to provide energy.

Step 1: Activation of phytanic acid

Although the first convincing evidence for the need for phytanic acid activation was provided by Watkins and co-workers in 1994 [20], there remains uncertainty in the literature regarding the location and enzymes responsible for phytanic acid activation. In order to facilitate further degradation, the fatty acid molecule is activated by the enzyme acyl-CoA synthetase. Initially, in fatty acid α-oxidation pathway, a β-methyl branched long chain fatty acid i.e phytanate that is present in plasma is taken up by the liver. It is activated to its coenzyme A (CoA) derivative in mitochondria, endoplasmic reticulum or peroxisomes. The reaction involves the attachment of Coenzyme A (CoA) to the fatty acid, resulting in the formation of fatty acyl-CoA. Adenosine triphosphate (ATP), which is hydrolysed to adenosine monophosphate (AMP) and inorganic pyrophosphate (PPi), is required for this process. This triggers the fatty acyl-CoA for the subsequent steps in the alpha oxidation pathway. The specific acyl CoA synthetase(s) involved are still unknown, but phytanate can be activated by the products of the genes ACSL1 and SLC27A2 (ACSVL1), as demonstrated for the rat [21] and human [22] enzymes, respectively. Phytanic acid activation by a distinct acyl-CoA synthetase had been suggested to be localized in peroxisomes in human liver and fibroblasts, but localized in mitochondria and microsomes in rat liver and fibroblasts [23]. However, studies by Watkins and co-workers have provided evidence against the existence of a distinct phytanoyl-CoA synthetase [21]. These authors demonstrated that ACSL1 has an affinity for phytanic acid by using an in vitro transcription/translation system to express the cDNA encoding the long-chain acyl-CoA synthetase (ACSL1) [21,23].

A mechanism to transfer phytanoyl-CoA beyond the peroxisomal membrane is necessary since the catalytic region of the enzyme acyl-CoA synthetase (ACSL 1) is exposed to the cytoplasm, suggesting that phytanoyl CoA synthesis takes place in the extra-peroxisomal space. An alternative mechanism would be the translocation of phytanic acid as free fatty acid across the peroxisomal membrane, followed by activation within the peroxisome. The feasibility of this route is demonstrated by the presence of human very-long-chain acyl-CoA synthetase (VLACS, encoded by the SLC27A2 gene), which has been found to face the peroxisomal matrix and is capable of activating phytanic acid [22].

Step 2: Hydroxylation of Phytanoyl-CoA

In this step in the alpha-oxidation pathway, the fatty acyl-CoA derivative i.e phytanoyl-CoA is hydroxylated in the peroxisome by the product of PHYH to produce a 2-hydroxy-fatty-acyl-CoA i.e. 2-hydroxyphytanoyl-CoA [3]. Fe2+, ascorbate, and 2-oxoglutarate are required for the 2-hydroxylation of phytanoyl-CoA [24]. The fatty acyl-CoA is activated and then hydrates, adding a hydroxyl group (-OH) to the molecule's alpha carbon position. A hydroxyl group is formed in the fatty acyl-CoA when the enzyme adds a water molecule across the double bond. The enoyl-CoA hydratase enzyme is responsible for catalyzing this reaction. Further assessments of phytanoyl-CoA hydroxylase (PhyH) in human liver revealed that it is highly active, localized in peroxisomes, and absent in liver biopsies from Zellweger syndrome individuals [25].

Step 3: Decarboxylation of 2-hydroxy-phytanoyl-CoA.

This step involves the decarboxylation of 2-hydroxy-phytanoyl-CoA. It was initially anticipated that pristanoyl-CoA would be the product of alpha-oxidation of phytanic acid, but unexpectedly, pristanic acid was found to be the end product [26]. 2-hydroxyphytanoyl CoA lyase (2-HPCL) is the enzyme responsible for catalyzing the decarboxylation of 2-hydroxyphytanoyl-CoA. The formation of a keto group (=O) at the alpha carbon position results from the oxidation process, which also involves the oxidation of the hydroxyl group introduced in the oxidation step. The enzyme 2-hydroxy acyl-CoA lyase mediates the reaction which catalyzes the removal of water from the 2-hydroxy acyl-CoA, resulting in the formation of an alpha-ketoacyl-CoA. Following this, the lyase encoded by the HACL1 gene cleaves the 2-hydroxy-fatty-acyl-CoA to provide formyl-CoA and a fatty aldehyde (i.e pristanal) that has been shortened by one carbon unit (i.e. an n-1 aldehyde) [27]. This finding has led to the hypothesis that enzyme lyase catalyzes the first conversion of 2-hydroxyphytanoyl-CoA to the fatty aldehyde pristanal and formyl-CoA. Indeed, pristanal was produced when human liver homogenate was incubated with 2-hydroxyphytanoyl-CoA [26]. The formation of pristanic acid upon the addition of NAD as a cofactor for a putative aldehyde dehydrogenase, which possibly catalyzing the subsequent dehydrogenation of pristanal, suggested that the proposed pathway might be realistic. Despite the fact that formate was previously shown to be produced in this step [28], it has recently been shown that formyl-CoA is the primary product of this decarboxylation [27, 29].

Step 4: Dehydrogenation of Pristanal

In the last step of alpha oxidation, phytanic acid alpha-oxidation involves the conversion of pristanal to pristanic acid. It has been shown that human liver and cultured skin fibroblasts both contain a NAD(P) dependent fatty aldehyde dehydrogenase which catalyzes this reaction [26,30]. Aldehyde dehydrogenase oxidises aldehyde to its corresponding fatty acid (e.g. pristanate). As the fatty acid is shortened through α-oxidation, it is once more activated to its CoA

ester. Although ACSVL1 can activate pristanate, it is unclear which isoform(s) of ASCL or ACSVL catalyzes this reaction. The hydrolysis of formyl-CoA produces formate, which is exported from the peroxisome into the cytosol and utilized in the metabolism of folate [22]. The possibility that this conversion occurs in the endoplasmic reticulum was proposed based on a single experiment conducted solely on human liver [26]. The potential contribution of the fatty aldehyde dehydrogenase ALDH3A2 was examined through the use of cell lines obtained from patients suffering from Sjögren Larssen syndrome (SLS), a disorder characterized by a microsomal ALDH3A2 deficit status [30].

Step 5: Catabolism of pristanic acid by the peroxisomal beta-oxidation system

Previously it has been demonstrated that pristanic acid is oxidized in peroxisomes rather than mitochondria [31]. Although, the site of activation of pristanic acid has not been established with certainty but may well be different depending on the source of pristanic acid. Indeed, early study had shown that pristanic acid can be activated at different subcellular locations including peroxisomes, mitochondria and endoplasmic reticulum. The activity localized in peroxisomes is membrane-bound, with the site of catalytic activity exposed to the cytosol [32]. Following uptake into peroxisomes from the cytosol, the shortened fatty acyl-CoA derivative (like pristanoyl-CoA) can go through limited peroxisomal β-oxidation, which can occur in three cycles for pristanoyl-CoA [33]. Three types of fatty acids are identified to endure limited peroxisomal β-oxidation: a very-long-chain fatty acid; a 2-methyl branched 2,3,4-saturated fatty acid (e.g. pristanate); and the bile acid synthesis intermediates (25*R*)-3α,7α-dihydroxy-5-β-cholestanate and (25*R*)-3α,7α,12α-trihydroxy-5β-cholestan-26-oate [11]. The products of peroxisomal β-oxidation are then shuttled into mitochondria and undergo further rounds of β-oxidation by either carnitine-dependent or carnitine-independent routes. These routes are tissue-dependent [3].

Significance of alpha oxidation of fatty acids

Alpha oxidation is an important metabolic pathway with more significance in the body. The major significances can be listed as: [19]

a. Energy production

The acetyl-CoA produced by the thiolysis of the dicarboxylic acid can enter the citric acid cycle, where it is oxidized to produce ATP.

b. Elimination of toxic metabolites

Fatty acids with an odd number of carbon atoms cannot be metabolized by beta-oxidation, and are metabolized by alpha oxidation, which produces dicarboxylic acids that can be excreted in the urine.

c. Role in lipid metabolism

This pathway is also involved in the synthesis of sphingolipids and long-chain fatty acids in different organisms. Other lipid molecules can also be formed from the dicarboxylic acids that alpha oxidation produces.

d. Regulation of fatty acid levels

The metabolism of fatty acids within the body may also be regulated by alpha oxidation. Fatty acid accumulation may result from pathway anomalies, and this could aggravate metabolic diseases like obesity and insulin resistance.

e. Role in developmental processes

Developmental processes may involve alpha oxidation. Previous studies have indicated that problems in brain, liver, and other organ development can result from gene alterations in this pathway [19].

Biochemical defect of alpha oxidation pathway

The discovery of considerably high levels of the branched-chain fatty acid phytanic acid due to defect in alpha oxidation pathway in certain individuals characterized Refsum disease as a disorder of lipid metabolism [34].

Refsum disease

Sigvald Refsum, in 1945, first identified Refsum disease (hereditary motor and sensory neuropathy type IV) which is a rare uncommon autosomal recessive condition. He originally nomenclated heredoataxia hemeralopica polyneuritiformis [35], and subsequently amended to heredopathia atactica polyneuritiformis. The main clinical manifestations reported by Refsum were retinitis pigmentosa, cerebellar ataxia, and chronic polyneuropathy; however, not all patients had cerebellar ataxia, as this condition progresses slowly [13].

In the early 1960s, when Klenk and Kahlke [12] reported the accumulation of an unusual 20-carbon, phytanic acid (3,7,11,15 tetramethyl- hexadecanoic acid), a branched-chain fatty acid present in a wide range of foodstuffs including dairy products, some meats and fish [36]. These findings characterized Refsum disease as an inborn error of lipid metabolism. Based on studies done since the 1960s, a defect in the breakdown of phytanic acid via alpha-oxidation leads to the accumulation of phytanic acid. The identification of the enzymatic defect in Refsum disease and its molecular basis, as well as the detection of genetic heterogeneity in Refsum diseases, were made possible by the resolution of the structure of the phytanic acid a-oxidation pathway [34].

Classification of Refsum disease

Refsum disease is divided into two distinct groups based on differences in the altered enzymes, metabolites accumulated, clinical manifestations, genetics and treatment.

- Classic/adult Refsum disease (CRD/ARD)

- Infantile Refsum disease (IRD)

Classic/Adult Refsum disease (CRD/ARD):

Adult Refsum disease (ARD), also referred to as "classic Refsum disease," is a peroxisomal disorder. It is also known as hereditary motor and sensory neuropathy IV or heredopathia atactica polyneuritiformism [37]. Classic Refsum disease is associated with the accumulation of phytanic acid in plasma and tissues [34]. The defective enzyme is phytanoyl-coenzyme A hydroxylase, which normally catalyses the second step in the breakdown of phytanic to pristanic acid using the CoA derivative as a substrate (the first step in alpha oxidation is the conversion of phytanic acid to phytanoyl CoA by Phytanoyl CoA ligase [38]. As a result, phytanic acid accumulates and appears in higher concentrations in the blood and other tissues like neurons and also in adipose tissue, myelin sheaths, kidneys, and liver occurs. It persuades impairment to the structural integrity of cells and tissues by interfering with covalent bonds, causing a wide range of symptoms [34].

Phytanoyl-CoA hydroxylase deficiencies, resulting from biallelic pathogenic variants in PHYH, is the primary cause in 90% cases. In ~10% of individuals, the disorder is milder and is associated with biallelic pathogenic variants in PEX7 [39]. The PHYH gene mutations induce an enzymatically inactive protein and dysregulate the degradation pathways, which accumulate phytanic acid. Mutations in PEX7 are typically seen with rhizomelic chondrodysplasia punctata but atypically can cause Refsum disease [40].

Clinical manifestations of ARD

Refsum disease equally affects men and women. The onset of CRD can occur as early as 2–7 years old, but it typically does not occur until early adulthood [37]. Symptoms are abundant, many of which overlap. A precise diagnosis relies significantly on the correlation of the clinical findings with a series of biochemical testing and genetic profiles. The following are the clinical signs and symptoms [37,41-43] seen in ARD are:

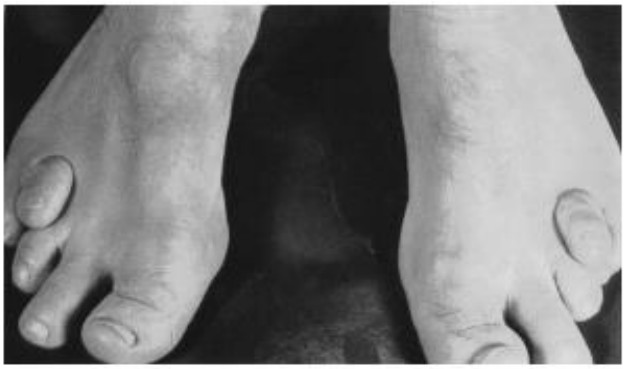
- Anosmia
- Ocular
- Polyneuropathy (sensory and motor)
- Sensori- neural deafness
- Pes cavus
- Ataxia
- Ichthyosis
- Pupillary miosis
- Nyctalopia
- Visual failure secondary to retinitis pigmentosa
- Gross constriction of the visual fields
- Cataracts and photophobia
- Short metacarpals and metatarsals present from birth
- Cardiac arrhythmias and cardiomyopathy
- Kidney malfunctioning
- Psychiatric disturbances
- Epiphyseal dysplasia

Figure 3| Shortening of the fourth toe in Refsum disease [44].

Laboratory Daignosis of ARD [37,39,45,46]

The approaches to establish the diagnosis of ARD are the clinical signs and symptoms, biochemical analysis of peroxisomal enzyme, plasma phytanic acid concentration, and molecular genetic testing.

- Elevated phytanic acid level >200 µmol/L (normal <30



µmol/L), unlike other peroxisomal disorders where levels are usually lower.

- Albuminocytologic differentiation of CSF and significantly elevated levels of phytanic acid
- A multigene panel for retinitis pigmentosa comprising PEX7, PHYH, and additional relevant genes.
- Phytanoyl-CoA hydroxylase enzyme activity in fibroblasts is measured.
- The amount of cellular phytanic acid alpha-oxidation (which is expected to be low in ARD); this process converts phytanoyl-CoA into 2-hydroxyphytanoyl-CoA can be measured Nevertheless, this test is not clinically available and cannot distinguish between ARD caused by variants in PHYH or PEX7.

Management of ARD

To appropriately treat indications and symptoms with antiarrhythmic and cardiogenic supportive medications, cardiac arrhythmias and cardiomyopathy require routine treatment from a cardiologist. The following measures to be taken in management of ARD are as listed below [37, 47-51].

- Dietary restrictions for avoiding foods high in phytols.
- A low-phytanic acid diet can be given orally or by nasogastric tube.
- If oral intake is restricted, appropriate parenteral nutrition & fluid therapies are needed to maintain plasma glucose concentrations & prevent ketosis.
- A high-calorie diet is necessary to avoid mobilization of stored lipids (including phytanic acid) into the plasma.
- Phytanic acid should be consumed no more than 10 mg per day in the diet, and fasting or rapid weight

loss should be avoided since these factors may stimulate lipolysis.

- Post-operative administration of parenteral nutrition with solutions deficient of phytanic acid such as soybean and egg yolk based formulas.
- A high calorie-phytate restricted diet can be provided during pregnancy Ibuprofen, amiodarone, and other medications should be avoided.
- Fish based oils are a better source of calories.
- Low vision aids are useful where & when required.
- Plasmapheresis or Therapeutic plasma exchange/TPE (frequently referred to as lipapheresis), is a procedure that is utilized when phytanic acid concentration requires to be reduced rapidly. It can also be performed serially out weekly. This technique inhibits down the progression of the disease but does not completely heal neurologic difficulties.

Prognosis of ARD

The prognosis of ARD is typically not favourable in absence of treatment. Severe cases or late diagnosis may be life-threatening. Arrhythmia and heart failure are the main causes of death [37,39].

Infantile Refsum disease (IRD)

Infantile Refsum disease (IRD) is a medical condition characterized by inherited genetic disorders that impair motor movements and cause damage to the brain's white matter. Multiple PEX-class enzyme deficits may occur, which may result in an accumulation of various substrates at once. These include lower plasmalogen levels in brain tissues and erythrocytes, as well as VLCFA, di- and tri-hydroxycholestanoic acid, pipecolic acid, and phytanic acid. It has been speculated that consequences of this dystrophy are caused by increased quantities of phytanic acid as well as other lipophilic intermediates intercalating into and disrupting retinal cell membranes [52]. However, with advancing age, phytanic acid levels can return to normal. Many symptoms resembling those of CRD are seen as a result of impaired phytanic acid and beta-oxidation of VLCFA, as well as decreased plasmalogen production. It can extant as prompt as the sixth month of infancy when the child shows indications of severe developmental delay. At least twelve distinct genetic loci have been linked to IRD. These loci include PEX1 (7q21.2), PEX2 (8q21.13), and PEX26 (22q11.21), which encode for ATPases, which imports of cytosolic proteins into peroxisomes [34,53]. In both cases, progressive visual loss occurs as a result of elevated phytanic acid levels that obstruct the retinal pigment epithelium's capacity to esterify vitamin A, contributing in an early diagnosis [54].

Clinical manifestations of IRD

Neonates with IRD typically present with hypotonia, large fontanels, failure to thrive, and cholestatic jaundice. IRD is characterized by developmental delay, delayed disease progression, and a risk for adult survival in some patients, dependent on the level of medical treatment. The various clinical features are as follows [37,42, 55-59].

- Visual impairment
- Hypotonia
- Cerebellar ataxia and gait
- Peripheral neuropathy
- Severe mental retardation
- Sensorineural deafness
- Rod-cone dystrophy
- Nyctalopia
- Retinitis pigmentosa
- Anosmia
- Nystagmus
- Slow Neurologic deterioration
- Growth retardation
- Spasticity
- Craniofacial dysmorphism

Some lesser observed findings are:

- Hepatomegaly with cirrhosis
- Seizures
- Cardiomyopathy
- Sporadic bleeding events
- Gastrointestinal manifestations including vomiting, diarrhea, and malabsorption

Laboratory Diagnosis of IRD [37,58, 60]

The diagnosis of IRD is established by combining the clinical signs and symptoms with molecular and biochemical tests, as well as macro- and microscopic inspections and peroxisome immunocytochemistry analysis.

- Following a physical examination, IRD is suspected; a biochemical evaluation establishes apparent diagnosis.
- Elevated plasma concentrations of C26:0 and C26:1, as well as elevated ratios of C24/C22 and C26/C22, are suggestive of abnormalities in peroxisomal fatty acid metabolism, as indicated by very-long-chain fatty acid (VLCFA) levels.
- Plasmalogens C16 and C18 concentrations in erythrocyte membranes are usually low but can occasionally be normal.
- The levels of bile acid intermediates (THCH and DHCA) and plasma pipecolic acid are elevated.
- In certain instances, VLCFA levels and enzymatic assays in fibroblasts can be within the normal range, necessitating further testing in specialized laboratories.
- The 13 PEX genes can be sequenced.
- Myelin alterations can be detected by MRI.

Management of IRD

Treatment for IRD is symptomatic and requires comprehensive management [61,62]. It is known to be incurable. There are minimal reports on how treatments affect the course of the disease. Reports have occasionally indicated, nevertheless, that dietary

modifications have particular biochemical impacts [63,64]. Due to the autosomal recessive inheritance, genetic counselling may be a possibility. The different possibilities of management can be as follows.

- Foods rich in phytanic acid should be restricted.
- An intermittent TPE in severe circumstances can be used.
- To provide appropriate calorie intake, a gastrostomy tube can be required.
- Cataracts should be removed in early infancy and glasses used.
- Individuals with hearing impairments should be given hearing aids, and cochlear implants may be an option when hearing loss is severe.
- Vitamin K supplements can be used to treat hepatic coagulopathy, and primary bile acid therapy can contribute to better liver function.
- Seizures are treated with standard epileptic drugs.
- Liver function, hearing, and vision changes are monitored throughout the span of an individual's life.

- Urea maintains the body hydration and helps in the hyperkeratosis-related removal of excess keratin. An additional choice is to apply hydrating moisturizers.
- For skin manifestations, several emollients and keratolytics might be used.
- Lactic acid, an alpha-hydroxy acid, has a keratolytic effect that makes comedones easier to release which is available in 5% and 12% strengths.

Prognosis of IRD

Despite being a fatal disease, some children with IRD can survive into their teens and twenties, and perhaps later in life. Significant variances can be observed in terms of life expectancy, medical problems, and neurological function. Many patients survive childhood, and survival to adulthood is possible [37].

CONCLUSIONS

α-oxidation results in the oxidative removal of the first carbon atom, the carboxyl group, of a fatty acid or carboxylic acid to yield CO2 and a fatty acid or carboxylic acid shortened by one carbon atom. It plays a significant role in the breakdown of branched-chain fatty acids. The phytanoyl-CoA hydroxylase deficiency that causes rare Refsum disease, an autosomal recessive disorder, results in an accumulation of phytanic acid levels because of defective alpha-oxidation. Early detection may help to diminish visual and auditory deterioration in Refsum disease, which is partially curable. Further, more specific therapies may be accessible eventually as the genetic and metabolic pathways of this rare disease remain to be explored.

ADDITIONAL INFORMATIONA AND DECLARATIONS

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Author's Contribution: Designed the framework of drafting the manuscript, reviewed different scientific literatures and scripted and revised all the versions of the draft with his intellectual content prior to publication**: SP**

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