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The Senses Disease: a Refsum adult disease case report and a revision of literature

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Abstract

Refsum Disease is a rare autosomal recessive error of lipid metabolism; onset of symptoms in "classic Refsum disease" or "adult Refsum disease" ranges from age seven months to after age 50 years. The identification of symptoms, that interest all the senses, is essential for the management. We briefly describe a case occasionally diagnosed in adult life and analyzed the main aspects of this rare disease.

Keywords: *Anosmia, Phytanic acid, Polyneuropathy, Refsum disease, Retinitis pigmentosa*

Abbreviations

ARD: Adult Refsum Disease

LDL: low density lipoproteins

OMIM: Online Mendelian Inheritance in Man

RD: Refsum Disease

RP: Retinitis pigmentosa

VLDL: very low density lipoproteins

1.Case report

Which is the mystery that may underlie the senses weakening not connected with aging? Is possible that exist a pathology involving all the senses? And that this pathology can manifest itself in the middle ages?

A 64 years old woman has been admitted to the hospital for an hip fracture occurred after a fall.

Collecting medical history a series of different symptoms has been recognized: a diagnosis of Retinitis Pigmentosa associated with cataract made at the age of 60, motor and sensory fibers axonal and demyelinating polyneuropathy with a proprioceptive and postural deficit, and bilateral neurosensorial hypoacusia. She objectively presents an abnormal of the foot toes and of the third finger of the right hand. The patient referred also an hypo-anosmia not clinically investigated and to the question of possible consanguinity of the parents she answered affirmatively.

Regarding all these symptoms a Refsum disease has been hypothesized and the genetic tests associated to the phytanic acid dosage confirmed the suspected diagnosis.

Table 1. Clinical features of the Refsum Disease.

Category	Subcategory	Features
Inheritance	-	Autosomal recessive
Head and Neck	Eyes	Sensorineural deafness, progressive
	Nose	Anosmia
Cardiovascular	Heart	Cardiomyopathy
		Cardiomegaly
		Cardiac failure (sudden death has been reported)
		Electrocardiographic abnormalities
Skeletal	-	Multiple epiphyseal dysplasia
	Hands	Shortening of the metacarpals
	Feet	Shortening of the metatarsals
		Pes cavus
Skin, Nails, Hair	Skin	Ichthyosis
Neurologic	Central Nervous System	Increased CSF protein with normal cell count
	Peripheral Nervous System	Peripheral sensorimotor neuropathy
		Hyporeflexia
		Limb atrophy
		Limb weakness
		Sensory impairment
		Nerve hypertrophy
Laboratory Abnormalities	-	Increased phytanic acid in body tissues and fluids
		Decreased phytanic acid oxidase activity
Miscellaneous	-	Affected infants appear normal
		Symptoms show insidious onset in the late first through third decades
Molecular Basis	-	Caused by mutation in the phytanoyl-CoA hydroxylase gene (PHYH, 602026.0001)
		Caused by mutation in the peroxisome biogenesis factor 7 gene (PEX7, 601757.0007)

From OMIM database for 266500 ICD+ REFSUM DISEASE, CLASSIC

2. Literature background

Refsum disease (RD) (ARD, OMIM # 266500) is an autosomal recessive inborn error of lipid metabolism classically characterized by a tetrad of clinical abnormalities: retinitis pigmentosa, peripheral neuropathy, cerebellar ataxia, and elevated protein levels in the cerebrospinal fluid without an increase in the number of cells. The incidence of RD thought to be less than 1:1.000.000 [1] although the exact incidence and prevalence of the disorder in the general population is not known. It usually becomes manifest before the age of 20. However, the disease has been diagnosed up to age 50. It's also known as phytanic acid oxidase deficiency, heredopathia atactica polyneuritiformis, hereditary motor and sensory neuropathy IV or HSMN4[2].

The disorder was first described in 1946 by Norwegian neurologist Sigvald Refsum (1907-1991) [3].

The biochemical defect was identified in 1963 by Kenke and Khahlke, who noticed the presence of excess phytanic acid in the plasma of affected patients [4]. The first case of RS in Italy was described in the 1965 [5]. Phytanic acid cannot be degraded by b-oxidation because of the presence of a 3-methyl group; instead it undergoes one round of a-oxidation that shortens phytanic acid by one carbon atom to give pristanic acid. Steinberg et al. postulated that adult RD results from a deficiency in the enzyme responsible for a-oxidation of phytanic acid [6].

Considered for a long time as a complex disorder with involvement of multiple systems, including the retina, the modern of the adult Refsum disease is that is the first and foremost a retinopathy in which additional symptoms may develop if not treated appropriately.

The full clinical picture includes retinitis pigmentosa (RP), hand-feet deformities, anosmia, sensorineural hearing loss, a chronic sensorimotor polyneuropathy, ataxia, ichthysosis and, in severe cases, cardiomyopathy [7].

Blindness and the complete loss of hearing prior to age 40 cause severe impairment to the patient's quality of life, and cardiac arrhythmias can be fatal. An early sign of the disease is retinal degeneration, found in all patients at the time of diagnosis. This cannot be distinguished from the isolated form of retinitis pigmentosa. Patients

complain of night blindness during childhood or adolescence. Later on, visual field constriction and attenuation of visual acuity emerge. Fundoscopy reveals attenuated retinal vessels and pigment epithelium degeneration; however, adult Refsum disease often lacks the typical spicular intraretinal pigmentation characteristic of retinitis pigmentosa [7] (Figure 1). In the majority of cases the isolated increase in the plasma level of exclusively phytanic acid is caused by the deficient activity of phytanoyl-CoA-hydroxylase (PHYH), a peroxisomal protein that catalyzes the first step in the a-oxidation of phytanic acid. In most patients adult Refsum disease is caused by mutations in the gene coding for phytanoyl-CoA hydroxylase, called PAHX (or PHYH).

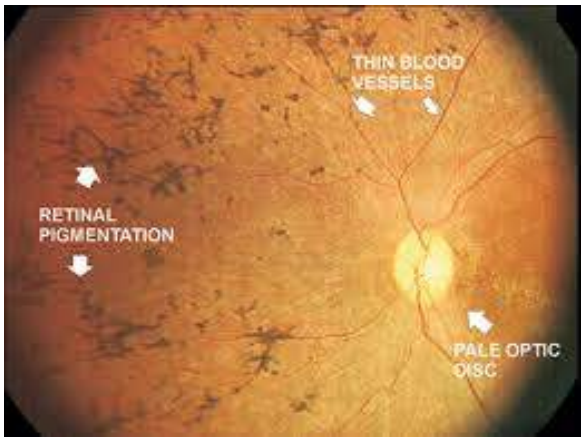

Figure 1. Retinitis pigmentosa.

Phytanic acid cannot be synthesized in the human body; it is solely derived from exogenous dietary sources as a byproduct of the degradation of chlorophyll. While chlorophyll in vegetables is a potential source of phytanic acid, it cannot be digested by humans. In contrast, ruminant animals, with the help of their gastric flora, are able to absorb the chlorophyll-bound phytol and metabolize it to phytanic acid. The main sources of phytanic acid are milk products and meat of ruminant animals, such as beef, lamb, and veal, as well as predatory fish (e.g., cod, tuna). The accumulation of phytanic acid in fatcontaining tissues, including nerves, brain, and adipose tissue, is considered to be the main culprit of the symptom complex of adult Refsum disease [7]. Adult Refsum disease is among those rare forms of retinal dystrophies for which a treatment is available. The aim of a therapeutic intervention in adult Refsum disease is to lower the body's content of phytanic acid.

Diets which are low in phytanic acid are extremely unpalatable and consequently regimens now include poultry, pork, fruit and vegetables [8]. Dietary restriction of phytanic acid in some cases is not sufficient to prevent acute attacks and stabilize the progressive course. Phytanic acid bound to large low density lipoproteins (LDL) and very low density lipoproteins (VLDL) molecules offers the possibility of extracorporeal elimination by lipid apheresis [9].

3. Discussion

RD is a rare condition that usually presents in late childhood with progressive deterioration of night vision but may also occur in the older ages with different and heterogeneous symptoms, whose strange common features are the senses involvement. The reduction of vision, hearing, smell, touch and proprioception [10] with the only preservation of taste, play a role of special interest in the management of the patient in particular from a rehabilitative point of view. The cortex motor organization need to receive different peripheral information especially coming from proprioception, vision and vestibules. When a reduction of one sense occur, others may compensate in order to make possible the action. In this case the decreased vision is followed by the proprioception impairment with a consequently fall.

The early and correct diagnosis is basic for the correct management of the syndrome but also to prevent the onset of the symptoms themselves; in particular when first diagnosing a tapetoretinal dystrophy, the ophthalmologist should consider adult Refsum disease as part of the differential diagnosis and specifically ask for associated manifestations [7]. In fact Wierzbicki et al [11] showed that in 15 individuals with RD the symptom founded in all the patients was exactly the Retinitis pigmentosa. Anosmia was the second symptom founded in 14 patients whose pathophysiology is uncertain but may be related to central sensory neurone-toxicity analogous to that found in photoreceptors and to a lesser extent in auditory neurons [12]. The other symptoms are less frequent (neuropathy 11/15, deafness 10/15, ataxia 8/15, ichthyosis 4/15) but however no less important for the diagnosis [13]. Considering the extreme rarity of this condition, the medical care of Refsum patients required interdisciplinary cooperation, also with patient organizations, in order to make an early diagnosis and to contain symptoms.

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