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Case report

X-linked adrenoleukodystrophy: are signs of hypogonadism always due to testicular failure?

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ABSTRACT

We present the clinical and hormonal findings of a young male with X-linked adrenoleukodystrophy (X-ALD), with special emphasis on the biochemical and clinical pattern of hypogonadism. A patient, with primary adrenal insufficiency since the age of 5 years, developed progressive neurological symptoms at the age of 29. Diagnosis of X-ALD was established by elevated serum very long chain fatty acids (VLCFAs) and genetic testing. His sexual body hair was sparse. Hormonal investigations revealed normal testosterone and inappropriately elevated LH levels. Androgen receptor gene analysis was negative for mutations or polymorphic variants associated with decreased receptor activity. Signs of hypogonadism in patients with confirmed X-ALD are not exclusively due to primary testicular failure. Tissue specific androgen resistance represents an alternative possibility. Since no loss-of-function mutations were detected in the androgen receptor, it is speculated that the patient's androgen resistance could be part of a functional defect mediated through VLCFA accumulation at the testosterone receptor and/or post-receptor levels.

Key words: Adrenomyeloneuropathy, Hypogonadism, Androgen resistance

INTRODUCTION

X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal disorder caused by defects of the ATP-binding cassette subfamily D, member 1(*ABCD1*) gene located in Xq28.[1] The gene product, ALD protein (ALDP), a member of the ATP-binding cassette transporter superfamily, is localized in the membrane of peroxisomes and participates in the peroxisomal degradation of very long chain fatty acids (VLCFAs).[2] Prevalence of X-ALD hemizygozity is estimated at 1:42,000 and that of hemizygocity and heterozygozity together at 1:16,000.[3] The biochemical abnormality underlying its clinical phenotype is impaired peroxisomal β-oxidation and accumulation

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of saturated very long chain fatty acids in the central nervous system white matter, adrenal cortex and testicular Leydig cells.

The clinical spectrum varies from a rapidly progressive cerebral childhood form, comprising about 35-40% of all cases, to a slowly progressive spinal adult form, adrenomyeloneuropathy (AMN), found in about 45% of patients. In 10% of affected males the only manifestation is adrenal insufficiency (Addison disease), while approximately half of the heterozygous females develop an AMN-like syndrome at an older age.[4] The childhood cerebral form may present with behavioral problems such as vision disturbances and cognitive impairment and may lead to total disability and death within 2 to 5 years from diagnosis.[5] AMN-affected males present with mild spastic paraparesis, impaired vibration sense, sphincter dysfunction or impotence in their third to fifth decade. Approximately 70% of AMN patients have already developed adrenocortical insufficiency[6] when neurological signs become apparent and an equal percentage have signs of testicular insufficiency.[7]

In this report we present the case of a young man diagnosed with adrenomyeloneuropathy. Sparse sexual hair, high normal testosterone levels and inappropriately elevated LH levels, indicating androgen resistance, were the main manifestations of impairment of the hypothalamus-pituitary-testicular axis.

CASE REPORT

A 29-year old patient was admitted to our department because of easy fatigue, weakness and progressive difficulty in walking of at least one year duration.

He was the first offspring of non-consanguineous parents of Caucasian origin (Figure 1). The patient was initially diagnosed with adrenal insufficiency when he was 5 years old. He visited our endocrine department 9 years ago and he was since re-evaluated annually. He was on replacement therapy with 20 mg hydrocortisone and 0.05 mg fludrocortisone daily. At his last visit he complained of easy fatigue and gait disturbance. He had no symptoms of cortisol excess (buffalo hump, weight gain, bruising, etc.) and no complaints of decreased libido or erectile dysfunction.

From his medical history he was found to be a hepatitis B carrier, as were his father aged 55 years and his younger brother aged 25 years. His mother aged 54 and a middle brother aged 27 years, who is married and has two young boys, aged 3 and 1 years old, were all healthy (Figure 1). The rest of his family history regarding first and second degree relatives was unremarkable.

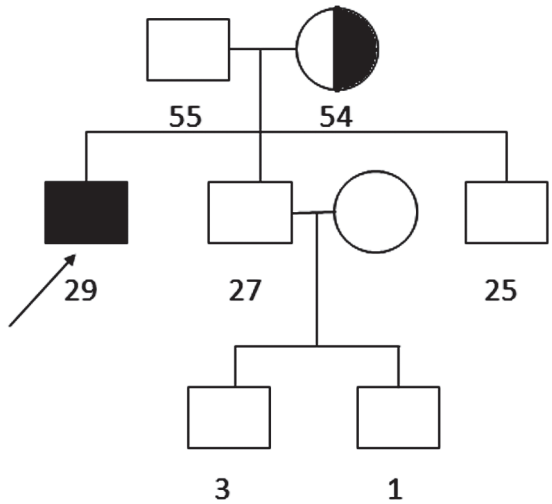

Figure 1. Genealogical tree of the studied family. Patient (arrow) is indicated by filled symbol and his heterozygous mother by a semi-filled one. Numbers under symbols indicate family members' ages. His brothers have not yet been checked.

On admission, physical examination revealed hyperpigmented skin lesions without stigmata of cortisol excess. Height was 166 cm and weight 59 kg with a BMI of 20.32 kg/m^2.The thyroid gland was unpalpable. His blood pressure was 100/60 mmHg in the upright and supine position. Sexual body hair was sparse (pubis: Tanner stage 4, axilla: Tanner stage 2); there was no facial hair (Figure 2). Testicular

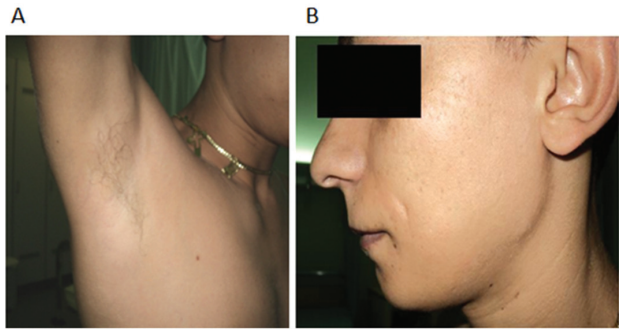

Figure 2. Patient's pictures: Terminal hair is sparse on axilla (A) and absent on face.

volume was estimated at 25 cc bilaterally. Penis and scrotum were normal. The mammary gland was not palpable bilaterally. On neurological examination, upper motor neuron signs of mild pyramidal pattern weakness affecting predominantly the lower limbs with brisk tendon reflexes and sustained knee clonus were observed. No sensory deficits were evident from examination.

Routine laboratory investigations revealed normal electrolyte profile suggestive of adequate mineralocorticoid supplementation. On blood counts, hemoglobin (Hb) was 14.3 g/dl, white blood cells (WBC) were 9.17 X 10^3/μl (neutrophils: 42%; lymphocytes: 44.7%) and platelets (PLT) were 282,000/μl. Liver enzymes were found elevated: aspartate aminotransferase was 177 IU/l (normal up to 37 IU/l) and alanine aminotransferase was 503 IU/l (normal up to 40 IU/l). Viral serology profile was compatible with chronic hepatitis B [hepatitis B surface antigen (HBsAg)+; hepatitis B core immunoglobulin G (anti-HBc IgG)+; hepatitis B e antibody (HBeAb)+] and measured viral load was found elevated; hepatitis B virus DNA (HBV-DNA): 2, 983, 900 copies/ml). On hormonal evaluation thyroid function tests were normal [free T4:1.27 ng/dl (16.34 pmol/l) with normal 0.9-1.7 ng/dl, TSH: 2.12 mIU/ml (normal 0.3-4 mIU/ml)], prolactin (PRL) was 19.9 ng/ml (0.85 nmol/;l) with normal up to 12.3 ng/dl, plasma ACTH levels were found profoundly elevated, 10,920 pg/ml (2,402 pmol/l) and active renin was 24.5 pg/ml (0.58 pmol/l; with normal 3-33 pg/ml). Notably, both adrenocortical and thyroid auto-antibodies were negative, Mantoux skin reaction was also negative and adrenal computed tomography (CT) revealed no pathology.

The constellation of neurological symptoms in this patient with Addison's disease led us to reconsider the cause of his adrenocortical insufficiency. In view of the late neurological deficits, AMN had to be considered as a possible diagnosis. We proceeded to the measurement of serum saturated VLCFAs which indeed was diagnostic of AMN [(hexacosanoic acid (C26:00): 4.89 μmol/l; tetracosanoic acid (C24:00): 70 μmol/l, normal ranges 0.45-1.32 μmol/l and 33-69 μmol/l, respectively). In order to evaluate central nervous system involvement, conventional brain magnetic resonance imaging (MRI) including T1-weighted (T1W), T2-weighted (T2W), fluid-attenuated inversion recovery (FLAIR) images and cervical and lumbar spine MRI were performed. T2-weighted brain MRI revealed symmetrical demyelinating lesions involving the parieto-occipital white matter bilaterally (Figure 3A), whereas no gadolinium-diethylene triaminepentaacetic acid (Gd-DTPA) enhancement was observed on T1-weighted images. Atrophy of the thoraco-lumbar cord was evident on spinal MRI (Figure 3B). The patient also underwent sensor and motor conduction studies, which showed reduced amplitudes of compound

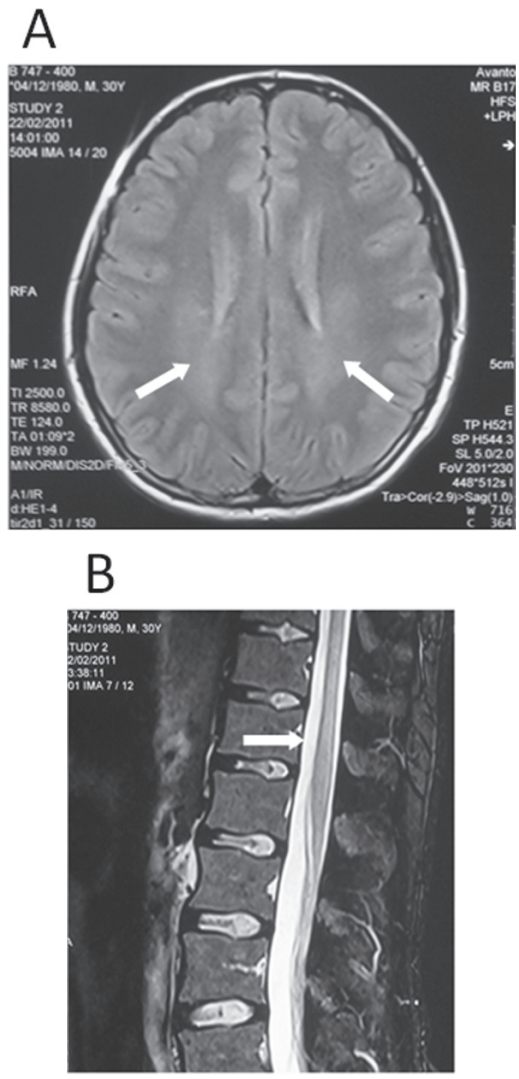

Figure 3. Brain and spinal cord MRI. A: Axial T2-weighted image showing increased signal in the parieto-occipital white matter bilaterally (arrows), indicating symmetrical demyelinating lesions. B: substantial atrophy of the thoracolumbar cord just above the conus medullaris (arrow) evident in a sagittal T2-weighted image.

motor action potentials (CMAP) and a prolongation in F-wave latencies of the peroneal nerve bilaterally. Diagnosis of adrenomyeloneuropathy was further confirmed by molecular genetic testing. Mutational analysis of the *ABCD1* gene revealed the point mutation c.521A>G in exon 1, causing the substitution of the amino acid tyrosine by the amino acid cysteine at codon 174 (Figure 4A). This is a previously reported missense pathogenic p.Tyr174Cys mutation.[8] Both brothers and the mother's first and second degree male relatives were scheduled for plasma VLCFAs determination. As expected, according to the pattern of inheritance, the mother was a carrier of the detected mutation and her serum very long chain fatty acids levels (C26:00 levels: 1.76 μmol/l; C24:00 levels: 80 μmol/l) were compatible with heterozygosity (Figure 1). His younger brothers who live in Canada and Albania have not yet measured plasma VLCFAs.

Assessment of gonadal function

In view of the patient's hypogonadal signs (Figure 2) and the known association of X-ALD with testicular dysfunction, detailed assessment of testicular function was performed. Testosterone levels were high normal: 760 ng/dl (25.8 nmol/l; normal 240-1000 ng/dl), with free testosterone 16pg/ml (55.5 pmol/l; normal 5.8-18 pg/ml), and dihydrotestosterone (DHT) 0.45 ng/ml (1.5 nmol/l; normal 0.1-0.5 ng/ml). Serum SHBG was 65.2 nmol/l (normal 10-70 nmol/l), FSH: 4.1 mIU/ml (normal 4.1-18.1mIU/ml and, LH was inappropriately elevated, 28 mIU/ml (normal 1.5-9.3 mIU/ml). Estradiol was 35 pg/ml (128 pmol/l; normal 10-40 pg/ml). Sperm count was $29X10^6$/ml.

Mutational analysis of the androgen receptor (*AR*) gene, an X-linked gene located in Xq12, by PCR amplification and direct sequencing detected the c.2319-78T>G (Figure 4B) polymorphic genetic variant in intron 5; this variant is of no clinical significance.[9] No pathogenic mutations were detected. Polymorphic CAG tandem-repeat number was 26 (data not shown).

DISCUSSION

VLCFAs are toxic to axonal and neuronal membranes, resulting in axonal loss and eventually neuronal degeneration.[10] Regarding adrenal involvement, VLCFAs were also suggested as being toxic to the adrenal cortex, resulting in apoptotic cell death.[11] Interstitial Leydig cells may be similarly affected.[12] An additional scenario might be that membrane rigidity

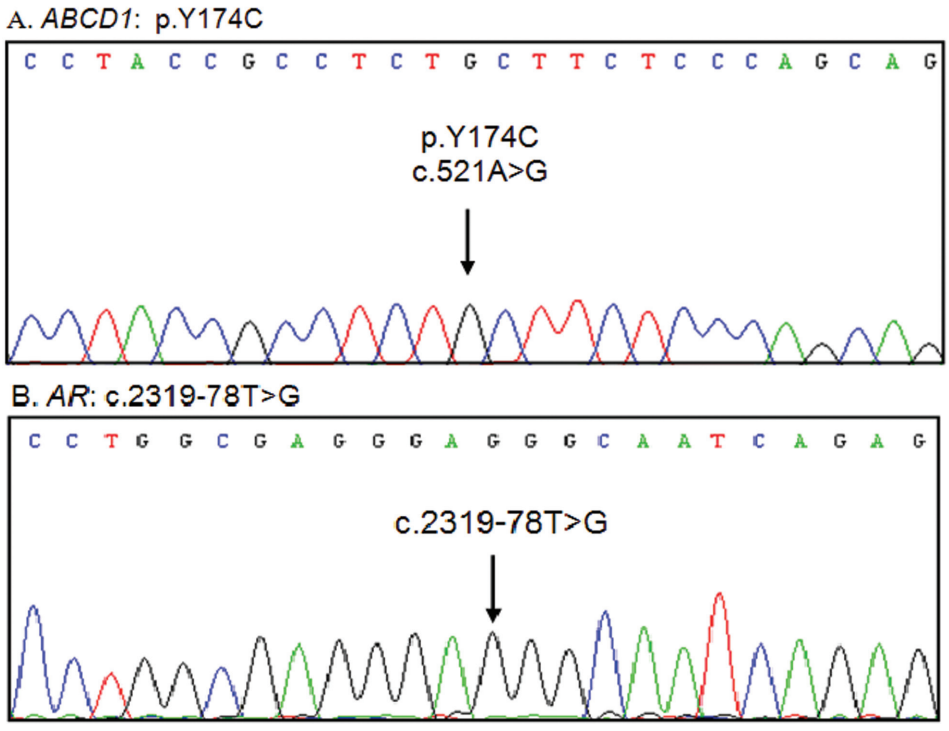

Figure 4. Results of the molecular analysis of the patient: **A.** ATP-binding cassette, superfamily D, member 1 gene (*ABCD1*) point mutation. The substitution of one base (TAC-TGC) results in the exchange of tyrosine for cysteine at codon 521 in exon 1 of *ABCD1*. **B.** Androgen receptor gene (*AR*) c.2319-78T>G polymorphic genetic variant in intron 5.

is increased by the incorporation of VLCFAs in cell membrane lipids, thus interfering with the receptor binding of ACTH, and possibly of FSH and LH.[13] Levels of VLCFAs, particularly C26:0 and C24:0, are elevated in all male patients and in most female carriers, although false negative or equivocal results occur in up to 20% in heterozygotes.[14]

In our patient, VLCFAs were elevated and molecular analysis further confirmed the diagnosis of X-ALD. The point mutation c.521A>G in exon 1 of the *ABCD1* gene found in this patient causes the substitution of the amino acid tyrosine by the amino acid cysteine at codon 174. The *ABCD1* gene located on chromosome Xq28 contains 10 exons encoding 745 amino acids. The *ABCD1* domain consists of a hydrophobic transmembrane domain (TMD) containing 6 a-helixes and a nuclear binding domain (NBD).[15] Mutations have been found throughout the entire gene, although there is a clustering of mutations in the NH2-terminal half of adrenoleukodystrophy protein (ALDP) including TMD1-6 and loop1-5 (40%), NBD (30%)[16] and exon 16, which has been identified as a mutational hot spot.[17] In the X-linked adrenoleukodystrophy database[18] to date 13011 mutations have been identified of which 610 (47%) are non-recurrent. Missence mutations represent 61% of all mutations. Different amino acid substitutions of the tyrosine 174 have been reported, namely, p.Tyr174His, p.Tyr174Asp, p.Tyr174Ser (www.x-ald.nl/accessed Oct 12, 2012).

There is no correlation between *ABCD1* gene mutations and clinical phenotypes.[18] The childhood cerebral form usually manifests between ages 4 and 8 years as attention deficit disorder or hyperactivity and progresses to impairment of cognition, behavior, vision, hearing and motor function. The second phenotype, adrenomyeloneuropathy, manifests commonly in the late twenties as progressive paraparesis, sphincter disturbances and sexual dysfunction.[19] Adrenal insufficiency manifests early often before the onset of neurological symptoms, most commonly between 5 and 10 years of age with weakness, unexplained vomiting and increased skin pigmentation due to excessive ACTH secretion.[20] Cerebral involvement is characterized by inflammatory myelinopathy with typically symmetrical parieto-occipital white matter lesions,[20-22] whereas in adrenomyeloneuropathy the main pathological feature is spinal cord long-tract distal axonopathy.[23,24] For adrenal insufficiency hormone replacement therapy is mandatory. For neuronal involvement therapeutic potentials include Lorenzo's oil,[5,25] bone marrow transplantation (BMT) when cerebral involvement is at an early stage,[26] up-regulation of other genes encoding proteins involved in alternative β-oxidation [adrenoleukodystrophy related protein (ALDRP), peroxisomal membrane protein 70 (PMP70), peroxisomal membrane protein 69 (PMP69)] by agents such as phenylbutyrate and lovastatin[20] and gene therapy.[27]

ALD-related hypogonadism has only been studied in a limited number of reports.[7,12,28,29] Clinical manifestations include decreased libido, erectile dysfunction and failure of the testes to descend. Half of the patients have diminished body sexual hair, one third gynecomastia and 12% testicular atrophy.[29] Although data are sparse, impairment of spermatogenesis is connected with the degree of progressive disorders but? with no significant decrease in fertility.[30] Assies et al[29] retrospectively studied 26 men with X-ALD and found that only 12% of them had low testosterone levels, the majority of whom exhibited an inadequate testosterone response to hCG stimulation. LH was elevated in 16% of the patients and FSH in 32%. LH response to GnRH administration was exaggerated in half of these patients.[29] Focusing on our patient, FSH levels were normal (4.1 mIU/ml) and testes were also normal both on physical examination and on ultrasonography; the patient's sperm count was $29X10^6$/ml. Normal FSH levels reflect normal spermatogenesis compatible with the normal sperm count, although even in cases with elevated FSH/LH levels and low testosterone levels integrity of seminiferous tubules is sufficiently maintained.[30]

We highlight the sparsity of terminal sexual hair along with testosterone levels close to the upper limit of the normal range [760 ng/ml (25.8 nmol/l)] and inappropriately elevated LH levels (28.3 mIU/ml) as the main findings of testicular dysfunction. Elevated LH with high normal testosterone levels along with diminished sexual body hair are consistent with decreased androgen action at least at the level of hypothalomo-pituitary feedback inhibition and sexual hair growth. In view of the normal penis growth, these findings are compatible with a tissue

specific pattern of androgen resistance. Mutational analysis was negative for pathogenic mutations of the androgen receptor (*AR*) gene located in the proximal long arm of the X chromosome; only a benign polymorphism (c.2319-78T>G) was detected in intron 5. In addition, the polymorphic CAG tandem-repeat number of 26 in exon 1 excluded spinal and bulbar muscular atrophy (Kennedy's disease), a rare X-linked recessive disorder where mutated AR (CAG-repeat number >40) results in androgen resistance and neurotoxicity.[31]

Although in our case the speculated defect might be independent of the X-linked ALD, for ALD patients with normal testosterone levels clinical signs of hypogonadism may be explained by the accumulation of VLCFAs in the cell hampering testosterone receptor and post-receptor events,[29] but this issue has not been fully elucidated. Treatment with Lorenzo's oil, despite significantly lowering the plasma concentration of VLCFAs, improved neither adrenocortical nor gonadal function.[32] An intratesticular accumulation and toxicity of VLCFAs not reflected by the concentrations in the circulation might explain this phenomenon.[33] It has also been suggested that some of these patients may benefit from androgen replacement therapy.[29,34] However, as in our case, androgen resistance may be a confounding factor.

In summary, we report a young man diagnosed with cerebral adrenomyeloneuropathy, highlighting that this rare disease merits consideration in all young males with Addison's disease, especially in those without other concurrent autoimmune disorders and in the presence of positive family history for neurological disorders. In addition, signs of hypogonadism in patients with confirmed X-ALD are not exclusively due to primary testicular failure. Androgen resistance represents an alternative possibility. It is speculated that this type of androgen resistance could be part of a functional defect in certain tissues mediated through VLCFA accumulation at the testosterone receptor and/or post- receptor levels.

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DECLARATION OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. Migeon BR, Moser HW, Moser AB, Axelman J, Sillence D, Norum RA, 1981 Adrenoleukodystrophy: evidence for X-linkage, inactivation and selection favoring the mutant allele in heterozygous cells. Proc Natl Acad Sci USA 78: 5066-5070.
2. Mosser J, Lutz Y, Stoeckel ME, et al, 1994 The gene responsible for adrenoleukodystrophy encodes a peroxisomal membrane protein. Hum Mol Genet 3: 265-271.
3. Bezman L, Moser AB, Raymond GV, et al, 2001 Adrenoleukodystrophy: incidence, new mutation rate, and results of extended family screening. Ann Neurol 49: 512-517.
4. Fatemi A, Barker PB, Ulug AM, et al, 2003 MRI and proton MRSI in women heterozygous for X-linked adrenoleukodystrophy. Neurology 60: 1301-1307.
5. Moser HW, Mahmood A, Raymond GV, 2007 X-linked adrenoleukodystrophy. Nat Clin Pract Neurol 3: 140-151.
6. Brennemann W, Kohler W, Zierz S, Klingmuller D, 1996 Occurrence of adrenocortical insufficiency in adrenomyeloneuropathy. Neurology 47: 605.
7. Brennemann W, Kohler W, Zierz S, Klingmuller D, 1997 Testicular dysfunction in adrenomyeloneuropathy. Eur J Endocrinol 137: 34-39.
8. Lachtermacher MB, Seuànez HN, Moser AB, Moser HW, Smith KD, 2000 Determination of 30 x-linked adrenoleukodystrophy mutations, including 15 not previously described. Hum Mutat 15: 348-353.
9. Gottlieb B, Beitel LK, Nadarajah A, Paliouras M, Trifiro M, 2012 The androgen receptor gene mutations database: 2012 update. Hum Mutat 33: 887-894.
10. Powers JM, 2001 Normal and defective neuronal membranes: structure and function: neuronal lesions in peroxisomal disorders. J Mol Neurosci 16: 285-287.
11. Powers JM, Schaumburg HH, Johnson AB, Raine CS, 1980 A correlative study of the adrenal cortex in adrenoleukodystrophy: evidence for a fatal intoxication with very long saturated fatty acids. Invest Cell Pathol 3: 353-376.
12. Powers JM, Schaumburg HH, 1981 The testis in adrenoleukodystrophy. Am J Pathol 102: 90-98.
13. Whitcomb RW, Linehan WM, Knazek RA, 1988 Effect of long-chain saturated fatty acids on membrane microviscosity and adrenocorticotropin responsiveness of human adrenocorticotropical cells in vivo. J Clin Invest 81: 185-188.

14. Moser HW, Moser AE, Trojak JE, Supplee SW, 1983 Identification of female carriers of adrenoleukodystrophy. J Pediatr 103: 54-59.
15. Kim WS, Weickert CS, Garner B, 2008 Role of ATP-binding cassette transporters in brain lipid transport and neurological disease. J Neurochem 104: 1145-1165.
16. Kemp S, Pujol A, Waterham HR, et al, 2001 ABCD1 mutations and the X-linked adrenoleukodystrophy mutation database: role in diagnosis and clinical correlations. Hum Mutat 18: 499-515.
17. Smith KD, Kemp S, Braiterman LT, et al, 1999 X-linked adrenoleukodystrophy; genes, mutations and phenotypes. Neurochem Res 24: 521-535.
18. Kemp S, Pujol A, Waterham HR, et al, 2001 ABCD1 mutations and the X-linked adrenoleukodystrophy mutation database: role in diagnosis and clinical correlations. Hum Mutat 18: 499-515.
19. Cappa M, Bizzarri C, Vollono C, Petroni A, Banni S, 2011 Adrenoleukodystrophy. Endocr Dev 20: 149-160.
20. Semmler A, Kohler W, Jung HH, Weller M, Linnebank M, 2008 Therapy of X-linked adrenoleukodystrophy. Expert Rev Neurother 8: 1367-1379.
21. Ito M, Blumberg BM, Mock DJ, et al, 2001 Potential environmental and host participants in the early white matter lesion of adrenoleukodystrophy: morphologic evidence for CD8 cytotoxic T cells, cytolysis of oligodendrocytes, and CD1-mediated lipid antigen presentation. J Neuropathol Exp Neurol 60: 1004-1019.
22. Ferrer I, Aubourg P, Pujol A, 2010 General aspects and neuropathology of X-linked adrenoleukodystrophy. Brain Pathol 20: 817-830.
23. Marino S, DeLuca M, Dotti MT, et al, 2007 Prominent brain axonal damage and functional reorganization in "pure" adrenomyeloneuropathy. Neurology 69: 1261-1269.
24. Powers JM, De Ciero DP, Masumi I, Moser AB, Moser HW, 2000 Adrenomyeloneuropathy: a neuropathologic review featuring its noninflammatory myelopathy. J Neuropathol Exp Neurol 59: 89-102.
25. Moser HW, Raymond GV, Kohler W, 2003 Evaluation of the preventive effect of glyceryl triolate- trierucate ("Lorenzo's oil") therapy in X-linked adrenoleukodystrophy: results of two concurrent trials. Adv Exp Med Biol 544: 369-387.
26. Peters C, Charnas LR, Tan Y, et al, 2004 Cerebral X-linked adrenoleukodystrophy: the international hematopoietic cell transplantation experience from 1982 to 1999. Blood 104: 881-888.
27. Cartier N, Hacein-Bey-Abina S, Von Kalle C, et al, 2010 Gene therapy for X-linked adrenoleukodystrophy using hematopoietic stem cells and a lentiviral vector. Bull Acad Natl Med 194: 255-264.
28. Aversa A, Palleschi S, Cruccu G, Silverstroni L, Isidori A, Fabbri A, 1998 Rapid decline of fertility in a case of adrenoleukodystrophy. Hum Reprod 13: 2474-2479.
29. Assies J, Gooren LJG, Van Geel B, Barth PG, 1997 Signs of testicular insufficiency in adrenomyeloneuropathy and neurologically asymptomatic X-linked adrenoleukodystrophy: a retrospective study. Int J Androl 20: 315-321.
30. Stradomska TJ, Kubalska J, Janas R, Tylki-Szymanska A, 2012 Reproductive function in men affected by X-linked adrenoleukodystrophy/adrenomyeloneuropathy. Eur J Endocrinol 166: 291-294.
31. Finsterer J, 2009 Bulbar and spinal muscular atrophy (Kennedy's disease): a review. Eur J Neurol 16: 556-561.
32. van Geel BM, Assies J, Haverkort EB, et al, 1999 Progression of abnormalities in adrenomyeloneuropathy and neurologically asymptomatic X-linked adrenoleukodystrophy despite treatment with "Lorenzo's oil". J Neurol Neurosurg Psychiatry 67: 290-299.
33. Aubourg P, 1997 The expanding world of primary adrenal insufficiencies. Eur J Endocrinol 137: 10-12.
34. Petroni A, Cappa M, Carissimi R, Blasevich M, Uziel G, 2007 Effect of testosterone metabolites on ABC half-transporter relative gene expression in X-linked adrenoleukodystrophy. J Inherit Metab Dis 30: 828.