X-linked adrenoleukodystrophy
The Saudi experience

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ABSTRACT

Objectives: To evaluate the clinical, biochemical, neuroradiological, and neurophysiological findings of patients with X-linked adrenoleukodystrophy.

Methods: Retrospective study evaluating the data of 10 X-linked adrenoleukodystrophy patients diagnosed at King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.

Results: The common presenting symptoms were deterioration in school performance, vision and hearing, behavioral changes, and seizures. Eight patients survived 1-4 years and one patient 12 years after the initial presentation, while one patient expired. Six patients had the childhood form, 3 had the adolescent form and one had the adrenomyeloneuropathy form. Six are in an advanced stage of the disease and 3 have mild to moderate spasticity. All except 2 manifested moderate to severe dementia with variable degrees of visual loss. Decreased hearing and features of adrenal insufficiency were seen in 7 patients. Very long chain fatty acids were significantly increased in seven and mildly elevated in 2 patients, however the C26 to C22 ratio was increased in all. The characteristic high-signal intensity of parieto-occipital white matter on brain magnetic resonance imaging T_2-weighted images was observed in all patients. Two patients had functional study of the brain, which showed hypometabolic activity in gray and white matter of the occipital lobes. Various neurophysiological abnormalities were detected. The response to different treatment modalities was not promising.

Conclusion: The disease is more common than had been previously recognized due to phenotypic variability and a wide spectrum of presentations. This report describes various aspects of this disorder and emphasizes the importance of early identification and treatment of asymptomatic but biochemically affected individuals, since all current therapeutic approaches are disappointing if overt neurological abnormalities have been already developed.

Keywords: X-linked adrenoleukodystrophy, clinical, biochemical, neuroradiological, neuro-physiological findings.

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This disease, as the name implies, is an X-linked recessively inherited disorder due to a defect in adrenoleukodystrophy (ALD) protein essential for the activity of peroxisomal very long chain acyl CoA synthetase (VLCAS), sometimes called lignoceroyl CoA ligase, an important enzyme in the peroxisomal β-oxidation of very long chain fatty acids (VLCFAs).[1-3]

Childhood ALD is characterized by a presymptomatic period that usually lasts from 4 to 8 years. This is followed by a period of behavioral changes and deterioration in intellect, vision and gait. Then a fairly progressive course ensues with spastic paraplegia, hemiplegia or quadriplegia, evolving into a terminal neurovegetative stage and, ultimately death, which typically follows 1 to 4 years after the disease onset.[4]

This disorder has a normal peroxisome structure

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and its biochemical abnormality is apparently only confined to metabolism of VLCFAs. It must not to be confused with neonatal adrenoleukodystrophy, another peroxisomal disorder with an autosomal recessive inheritance and significantly diminished peroxisomes and peroxisomal enzymes.[5,6]

Several reports have described this disease from different parts of the world. We document the occurrence of X-ALD in Saudi Arabia and report the clinical, biochemical, neuroradiological and neurophysiological findings, as well as the response to different treatment modalities tried in 10 patients. The aim of this study is to increase awareness of this lethal disease among physicians and encourage an early referral for complete diagnosis, potential therapy, and screening of asymptomatic individuals and genetic counseling.

Methods. ***Clinical analysis***. The medical records of 10 patients diagnosed with X-ALD by the inborn errors of metabolism section at KFSH & RC, a tertiary referral centre for neurometabolic diseases in the Kingdom of Saudi Arabia, were reviewed. Informations obtained included age at presentation, current age, presenting symptoms, current status of the patients, and detailed neurological findings. A history of consanguinity, affected siblings or other family relatives by the same disease, and finally, response to different forms of therapy, were also included.

Laboratory analysis. Biochemical analysis. Cortisol and adrenocorticotropic hormone (ACTH) were measured diurnally at least twice in each patient. Plasma levels of VLCFAs were measured by selective ion monitoring gas chromatographic/mass spectrometric assay (SIM-GC/MS), as previously described.[7,8] Dermal fibroblasts obtained from 3 patients and unrelated controls were used for biochemical assays of β-oxidation of lignoceric acid and dihydroxyacetonephosphate acyltransferase (DHAPATase), as previously described.[1,9]

Neuroradiological studies. Magnetic resonance imaging (MRI) of the brain was performed in all patients using a 1.5-T Picker Vista unit. Axial T_1-weighted (600/20) and T_2-weighted (2000/40,80) sequences, and T_1-weighted sagittal 4-mm contiguous slices were routinely obtained.[10] Fluorine-18 labeled 2-fluoro-2-deoxyglucose positron emission tomography (FDG PET) of the brain was performed in 2 patients. The fluorine-18 was produced in-house, using a 30 MeV cyclotron and fluorine-18 labeled 2-fluoro-2-deoxyglucose (FDG) was produced using a commercial automated synthesis technique. The patients were studied after fasting. Normoglycemia was confirmed prior to injection. Images reconstructed at a slice thickness of 0.3375 cm were then analyzed directly on the computer monitor.[11]

Neurophysiological studies. Electroencephalography (EEG) was recorded with surface electrodes placed according to the international 10-20 system using 18-channel electroencephalographs. Brainstem auditory-evoked potentials (BAEP) were recorded in response to 100 (μs rarefaction clicks delivered to each ear in turn. The majority of visual-evoked potentials (VEP) were recorded in response to bi- or mono-ocular 1 Hz red light-emitting diode goggle stimulation. Somatosensory-evoked potentials (SEP) were recorded in response to electrical stimulation of the median and tibial nerves at the wrist and behind the medial malleolus, and recorded from the contralateral somatosensory hand area (C3'/C4') and Cz' (median and tibial nerve stimulation), referenced to Fpz'. The motor nerve conduction (MNC) velocity was either measured from the median or peroneal nerves or both after surface electrical stimulation of the nerves at the wrist, elbow, ankle and fibular head. For the sensory nerve conduction (SNC), the sural nerve was stimulated behind the lateral malleolus and the sensory nerve action potential was recorded from the mid-calf.[12] The EEG and VEP were performed in all, BAEP in 7, SEP in 3, and MNC and SNC in 4 patients.

Results. ***Clinical findings.*** Clinical findings are presented in Table 1. The age of presentation varied widely among the patients, ranging between 5 and 16 years of age and the common clinical symptoms were deterioration in school performance, vision and hearing, behavioral changes, and seizures. Early psychomotor development was normal in all. The parents noticed darkening of skin color as the only abnormal initial finding in 3 patients. Eight patients survived 1 to 4 years and 1 patient 12 years after the initial presentation, while one patient expired. Currently, 6 patients are in an advanced stage of the disease; 3 have mild to moderate spasticity. All except 2 manifest moderate to severe dementia and pyramidal tract signs, and variable degrees of visual loss with optic atrophy. Decreased hearing and features of adrenal insufficiency were seen in 7 patients. The family history of 6 patients revealed at least 1 other male member to be affected by the same disease (Figure 1).

Biochemical findings. Biochemical findings are presented in Table 2. Biochemical evidence of adrenal gland dysfunction was documented in 9 patients. However, only 7 had the typical clinical findings seen secondary to adrenal gland insufficiency (Table 1 and Figure 2). The VLCFAs (C26) and the ratio of C26/C22, the cornerstone for the diagnosis of X-ALD, were determined in all except one patient, who was lost to follow-up. The C26 concentration was significantly increased in

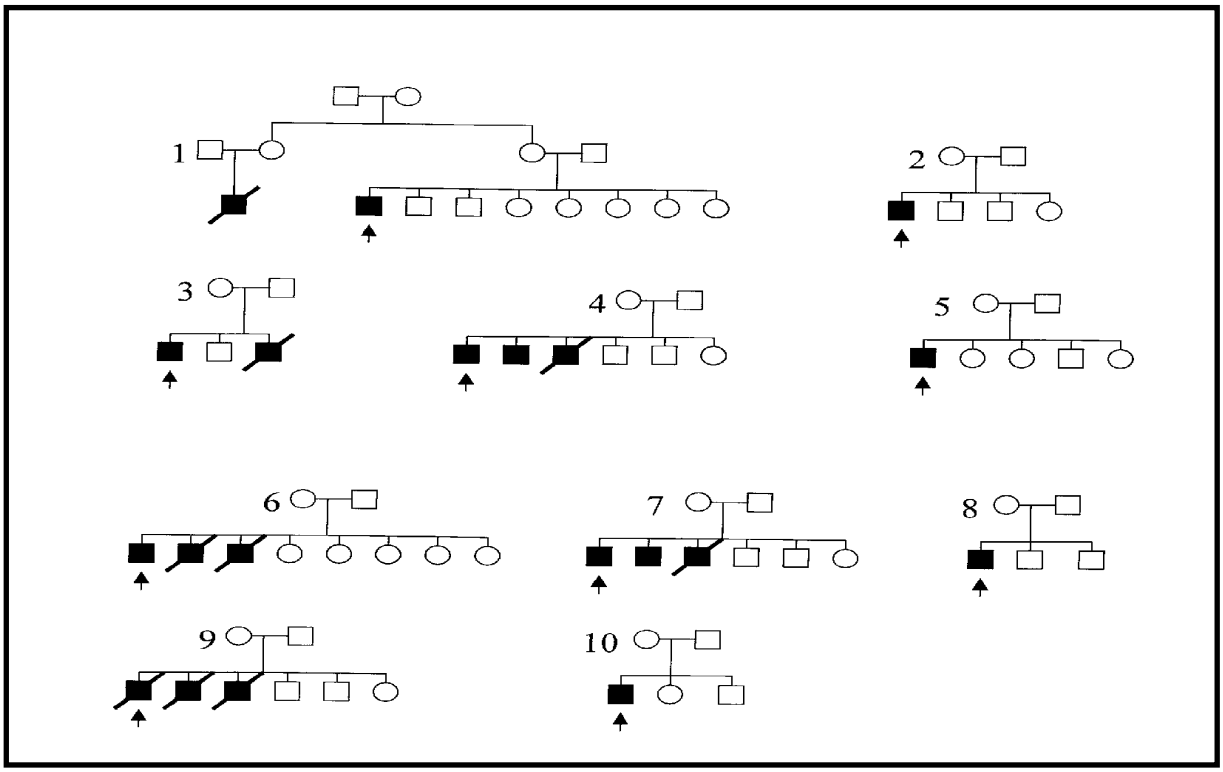

Figure 1 - Family pedigrees of X-ALD patients diagnosed at King Faisal Specialist Hospital and Research Centre. The numbers refer to the patient's numbers. At least one male member appears to be affected by the same disease in 6 families.

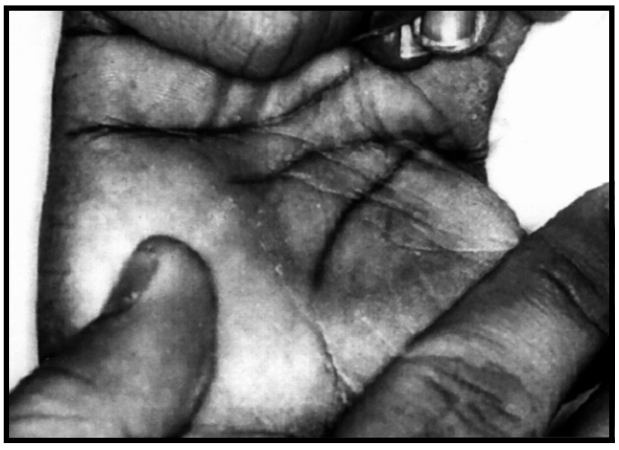

Figure 2a - Increased pigmentation secondary to adrenal insufficiency of skin creases of the hand.

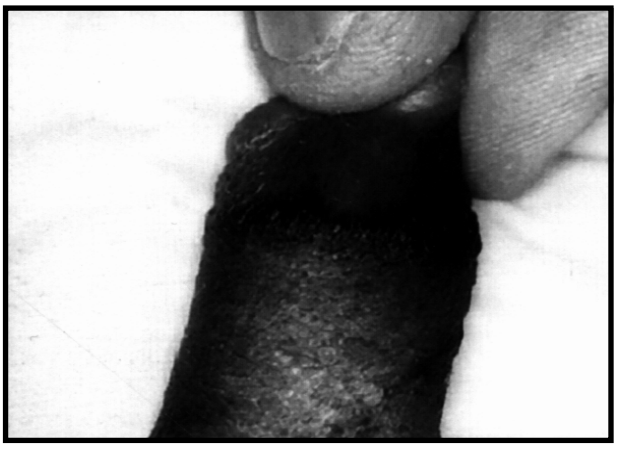

Figure 2b - Increased pigmentation secondary to adrenal insufficiency of the scar of the previously removed penile prepuce.

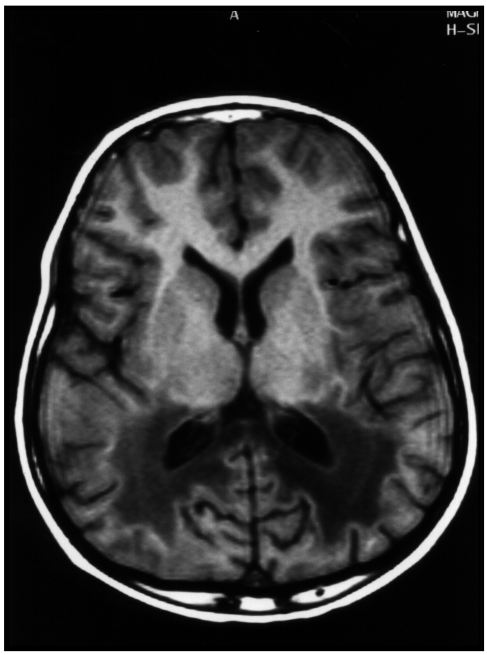

Figure 3a - The MRI of the brain shows the characteristic low and high intensity signals of the abnormal parieto-occipital white matter on T_1 weighted images.

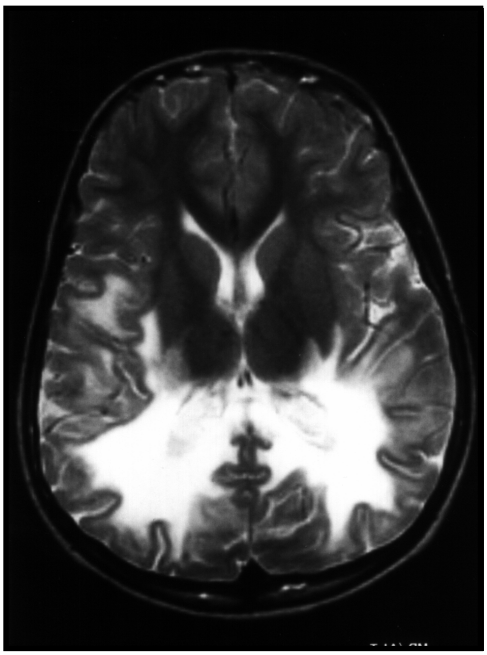

Figure 3b - The MRI of the brain shows the characteristic low and high intensity signals of the abnormal parieto-occipital white matter on T_2 weighted images.

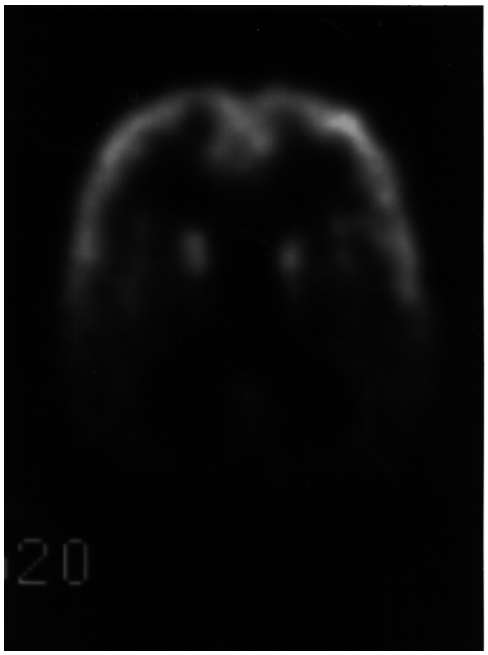

Figure 4 - The FDG PET scan of the brain shows hypometabolic activity in the cerebral cortex and white matter of the occipital lobes.

Table 1 - Clinical data of X-ALD patients diagnosed at King Faisal Specialist Hospital and Research Centre.

	Age of presentation	Current age	Presenting symptoms	Current status	Mental retardation	Pyramidal tract signs	Vision	Fundal exam	Hearing	Clinical evidence of adrenal insufficiency
Patient #1	11 years	15 years	School failure, gradual loss of vision and hearing	Spastic, blind with seizure disorder	Moderate	++	Blind	Optic atrophy	Decreased	Yes*
Patient #2	5 years	7 years	Seizure, gradual loss of speech, vision and hearing	Bedridden in terminal neurovegetative state	Profound	+++	Poor	Optic atrophy	Decreased	No*
Patient #3	16 years	28 years	Seizure, progressive paraparesis	Bedridden in terminal neurovegatative state	Moderate	+++	Poor	Optic atrophy	Normal	No*
Patient #4	7 years	11 years	Darkening of skin color	Adrenal insufficiency, mild spasticity	No	+	Normal	Normal	Normal	Yes*
Patient #5	11 years	13 years	Behavioral chances, seizure	Spastic, blind	Moderate	+++	Blind	Optic atrophy	Deaf	Yes*
Patient #6	7 years	10 years	Deterioration in school performance	Bedridden in terminal neurovegetative state	Moderate	+++	Poor	Optic atrophy	Decreased	No*
Patient #7	5 years	9 years	Darkening of skin color	Adrenal insufficiency mild spasticity	No	+	Normal	Normal	Normal	Yes*
Patient #8	12 years	14 years	Deterioration in school performance and progressive visual loss	Spastic, blind	Moderate	++	Blind	Optic atrophy	Decreased	Yes*
Patient #9	8 years	Expired (11 years)	Behavioral chances, darkening of skin color and hearing loss	Expired	Moderate	+++	Poor	Optic atrophy	Decreased	Yes*
Patient #10	5 years	8 years	Darkening of skin color	Adrenal insufficiency, moderate spasticity and	Moderate	+++	Poor	Optic atrophy	Decreased	Yes*

*Biochemical evidence of adrenal glands involvement (low cortisol and high adrenocorticotropic hormone). #=Number

Table 2 - Plasma levels of very long chain fatty acids (VLCFas) and C26/C22 ratio in X-ALD patients.

	VLCFAs (C26) (Normal: 0.248+/- 0.124 ug/ml)+	C26/C22 ratio (Normal: 0.007+/- 0.004)+
Patient #1	1.38	0.176
Patient #2	1.18	0.118
Patient #3	0.33	0.04
Patient #4	1.26	0.11
Patient #5*	-	-
Patient #6	1.309	0.117
Patient #7	0.97	0.08
Patient #8	0.38	0.06
Patient #9	0.928	0.063
Patient #10	1.667	0.163

*VLCFA not determined, the patient lost to follow-up. +From Moser et al. In: "Techniques in Diagnostic Human Biochemical Genetics: A Laboratory manual" 1991; 177-191.

seven and mildly elevated in 2 patients. However, the ratio of C26/C22 was abnormally high in all patients. The enzymatic studies performed on dermal fibroblasts from 3 patients showed a marked decrease in β-oxidation of lignoceric acid as compared with the control dermal fibroblasts; however, DHAPATase activity was normal, which further confirmed the diagnosis.

Neuroradiological and neurophysiological findings. Neuroradiological and neurophysiological studies are shown in Table 3. All patients showed the characteristic abnormal intensity signals in the parieto-occipital white matter on T_1-and T_2-weighted brain MRI images (Table 3, Figure 3). Two patients had FDG PET studies of the brain and these showed hypometabolic activity in both the cerebral cortex and white matter of the occipital lobes (Figure 4).

The electroencephalographic studies (EEG) were abnormal, with slow encephalopathic background activity and occasional sharp waves at the temporo-occipital region in 9 of the 10 patients studied. The BAEP studies were abnormal in 3 out of 7 patients studied, predominantly due to prolonged/absent wave V latency. The VEP was abnormal in 7 out of the 10 patients studied, due to absent or predominantly prolonged P100 latency. The SEP was abnormal in 1 out of 3 patients studied, due to absent cortical but normal spinal potentials. The MNC and SNC were prolonged in 3 out of 4 patients studied (Table 3).

Discussion.

X-ALD and its phenotypes. The term adrenoleukodystrophy (ALD) is used to describe 2 genetically determined disorders that are associated with loss of function of the adrenal cortex and destruction of the myelin in the central nervous system. Two types of ALD must be distinguished. One is an X-linked disorder with normal peroxisomal structure and a biochemical abnormality confined to VLCFAs metabolism. The other disorder, neonatal

Table 3 - Neuroradiological and neurophysiological data of X-ALD patients diagnosed at King Faisal Specialist Hospital and Research Centre.

	MRI	PET	EEG	BAEP	VEP	SEP	MNC	SNC
Patient #1	Abnormal	-	Abnormal	Abnormal	Abnormal	Abnormal	Abnormal	Abnormal
Patient #2	Abnormal	-	Abnormal	Normal	Abnormal	-	-	-
Patient #3	Abnormal	-	Abnormal	-	Abnormal	-	Abnormal	Abnormal
Patient #4	Abnormal	-	Abnormal	Normal	Normal	Normal	-	-
Patient #5	Abnormal	Abnormal	Abnormal	Abnormal	Abnormal	-	Abnormal	Abnormal
Patient #6	Abnormal	-	Abnormal	-	Abnormal	-	-	-
Patient #7	Abnormal	-	Abnormal	Normal	Normal	-	-	-
Patient #8	Abnormal	-	Abnormal	Abnormal	Abnormal	Normal	Normal	Normal
Patient #9	Abnormal	-	Abnormal	-	Abnormal	-	-	-
Patient #10	Abnormal	Abnormal	Normal	Normal	Normal	-	-	-

MRI: Magnetic resonance Imaging (abnormal: high-intensity signal of the abnormally bright parieto-occipital white matter); PET: Positron Emission Tomography (abnormal: hypometabolic activity in the occipital white matter and cerebral cortex); EEG: Electroencephalography (abnormal: slow encephalopathic background activity with occasional sharp waves at the temporo-occipital region); BAEPs: Brainstem Auditory Evoked Potentials (abnormal: predominantly due to prolonged/absend wave V latency); VEPs: Visual Evoked Poetentials (abnormal: absent or predominantly prolonged P 100 latency); SEPs: Somatosensory Evoked Potentials (abnormal: absent cortical but normal spinal potentials); MNC: Motor Nerve Condition and SNC: Sensory Nerve Conduction (abnormal: prolonged conduction time).

adrenoleukodystrophy has an autosomal recessive mode of inheritance, is associated with significantly diminished peroxisomes and impaired function of multiple peroxisomal enzymes.[5,6]

X-ALD (McKusick 300100) is the most frequent peroxisomal disorder and genetically inherited demyelinating disease.[5] Siemerling and Creutzfeldt gave the first clear description of the disease in 1923.[13] In 1963, Fanconi et al suggested X-linked recessive inheritance of a syndrome of Addison disease and cerebral sclerosis.[14] A potentially important observation was by Igarashi et al, they found that cholesterol esters in the brain and adrenals of these patients had an unusually high proportion of fatty acids with a chain length of 24-30 carbon atoms, rather than the usual length of less than 20.[15]

There are several distinct phenotypes attributable to X-ALD. The childhood form is the most common. Affected boys develop normally until 4 to 8 years when they suffer a progressive neurologic deterioration manifested as developmental regression, dementia, sensorimotor and psychointellectual dysfunction and generalized spasticity leading to a terminal neurovegetative state. Six of our patients had this form of the disease (patients 2, 4, 6, 7, 9 and 10); 2 with mild central nervous system involvement, one in a fairly advanced stage, 2 in a terminal neurovegetative stage, and one expired. The adolescent ALD is a progressive disease, with symptoms starting between the age of 11-21 years. Patients 1, 5 and 8 had this form of the disease and are currently spastic and blind. The third type is adrenomyeloneuropathy (AMN) (patient 3) which presents in late adolescence or early adulthood with a slowly progressive spastic paraparesis and sphincteric disturbance due to spinal cord involvement. Less common forms include an adult cerebral type with psychiatric symptoms and finally asymptomatic or presymptomatic persons, who have the biochemical defect but who are free of symptoms.[5] It is of interest that these variants occur regularly within the same kindred, so the phenotypic variation cannot be attributed to different genetic mutations.[16]

Intellectual deterioration, behavioral changes, and visual impairment in this period of life may be attributed to, or confused with, other neuro-degenerative disorders, such as metachromatic leukodystrophy, Wilson disease, subacute sclerosing panencephalitis or neuronal ceroid lipofuscinosis.[4]

More than 90% of childhood X-ALD patients have adrenal insufficiency. Commonly atrophy of adrenal cortex and deterioration in its function precede the onset of neurodegeneration.[17-19] For this reason, caution must be exercised in the interpretation of "isolated Addison disease" as a separate entity in young males, even though no neurological involvement or family history may be recorded.[20] In this report, nine of the 10 patients had the biochemical abnormalities characteristic of Addison's disease, but only 7 manifested the disease clinically (Table 1, Figure 2).

The full-blown picture of X-ALD is confined to males and patient's mothers and their carrier sisters are obligate heterozygotes. Nevertheless, 12-40% of female carriers show various degrees of neurological disability, although almost always milder than in the hemizygous male;[16] adrenal insufficiency is rare, and furthermore in 10-15% of those carriers overt neurologic disabilities develop only towards their middle life.[5,21,22]

Biochemical findings. The disorder is biochemically characterized by the accumulation of unbranched saturated fatty acids with a chain length of 24-30 carbons, particularly hexacosanoate (C26), as was seen in our patients. These toxic compounds most strikingly accumulate in the cholesterol ester and ganglioside fractions of brain white matter and adrenal cortex, although they are present to varying degrees in virtually all tissues and body fluids.[5,23]

Diagnosis of X-ALD hemizygotes is based on demonstration of a characteristic pattern of increased VLCFAs level in the plasma, red blood cells, or cultured skin fibroblasts. These diagnostic techniques also permit identifying 85% of heterozygotes, which can reach up to 100% if VLCFAs analysis is combined with DNA linkage studies. Assay of VLCFAs in cultured amniocytes or chorionic villous biopsy samples permits precise prenatal detection of affected fetuses. DNA linkage study can also be used to further augment the accuracy of the diagnosis.[5,24-26]

Neuroradiological findings. The most common initial objective evidence that suggests the diagnosis of childhood X-ALD is the striking and characteristic abnormalities involving the cerebral white matter with respect to location and attenuation patterns, as observed on CT or MRI studies of the brain, even relatively early in the course of the illness. The lesions are symmetric and involve the periventricular white matter in the posterior parietal and occipital lobes (Figure 3). The white matter changes progress relentlessly in caudorostral direction. Non-classical presentations with frontal lobe lesion,[5] calcifications within hypodense lesion,[27] and unilateral lesions have been previously reported.[28] The MRI is superior to CT scan in providing a clearer distinction between normal and abnormal white matter and in permitting better delineation of the subcortical lesions. Analysis of MRI images also permits precise structure-function correlation of the lesions of auditory or visual pathways. The disease in the auditory pathway is characterized by the involvement of the lateral lemniscus and medial geniculate body and in the visual pathway disease by the involvement of the lateral geniculate body, Meyer loop, and optic

radiation.[27] The contrast-enhanced ribbons found at the periphery of low-intensity signal plaques after gadolinium injection are of pathognomonic value in contrast-enhanced MRI. These areas of blood-barrier disruption on a background of inflammation and active demyelination appear on T_2-weighted sequences as ribbons of low-intensity signal within plaques of high-intensity signal.[29] Recently, brain MRI spectroscopy has demonstrated an increase in choline and lactate, and a reduction in N-acetyl aspartate in X-ALD patients. This modern technique is a more sensitive indicator of early neurological involvement than the conventional MRI and, therefore, it is more useful in assessing demyelination, by which therapeutic approaches can be judged.[30]

FDG PET scan has been found to be a sensitive indicator of altered brain metabolism in diverse pathologies of the central nervous system.[11,31,32] The findings in 2 patients indicate hypometabolic activity of the white matter and cerebral cortex in the occipital areas and in particular, in the visual cortex. These changes morphologically corresponded to the "burned out" lesions observed on MRI and were well correlated with the pathological findings previously described.[33]

Neurophysiological findings. Various neurophysiological studies have been performed in our patients (Table 3). The EEG was found to be abnormal in 90% of our patients, as previously described.[34] This was characterized by slow encephalopathic background activity and occasional sharp-wave discharges at the temporo-occipital region. The hearing was clinically decreased in 7 patients. In those, 3 out of 5 tested and had abnormal BAEP due to prolongation of wave V, a common abnormality detected. A similar percentage of abnormal BAEP was noted earlier.[35] As reported by Krivit et al,[36] and in this report, 70% of boys with X-ALD have prolonged VEP latencies. The SEP was abnormal in one out of 3 patients studied. The MNC and SNC velocities were prolonged in 75% of patients studied, reflecting peripheral nerve involvement.[37] With the magnitude and frequency of the neurophysiological abnormalities observed in X-ALD, we believe that neurophysiological tests have a place in the functional assessment of the structural lesions demonstrated by neuroimaging procedures and are important in monitoring the treatment response.

Genetics. The gene for X-ALD has been mapped to Xq28 (studied in patient 7). It is postulated that the ALD gene is involved in the import or anchoring of VLCFAs or a cofactor required for synthetase activity into the peroxisome.[5,38,39] So far, 110 mutations have been identified in the ALD gene, approximately 50% of which are missense mutations. No simple correlation between the genotype and phenotype could be established. However, once a mutation is found, it should be traced in all at-risk individuals of that family.[26,40,41] Close linkage of the ALD gene to the cluster of color blindness genes is indicated by the increased frequency of color-blindness in affected males and by the demonstration of deletion of cone pigment genes through the use of DNA probes, suggesting contiguous gene defects.[42,43]

Treatment. Treatment of a patient with X-ALD poses a great challenge to both the physician and the patient's family. After confirming the diagnosis, the patient needs a comprehensive management program involving partnership between the family, physician, visiting nurses, dietician, school authorities, and counselors.[44] Supportive therapy of the progressive neurologic disturbances is essential, such as modulation of the muscle tone, support of bulbar muscular function and feeding difficulties, physiotherapy, treatment of seizure, etc. Adrenal hormone replacement therapy is effective in correcting the adrenal insufficiency.

Several therapeutic strategies have been implemented, but at present there is no proven method of preventing or ameliorating the neurologic manifestations once they occur.[5] Dietary restriction of VLCFAs has failed to lower plasma VLCFAs or alter clinical progression.[45] This is because VLCFAs are derived mainly from endogenous synthesis. These observations led to the design of a diet that combined the oral administration of glyceryl trioleate (GTO) or glyceryl trierucate (GTE) or in a mixture of 4:1 of GTO/GTE, "Lorenzo's oil", to compete with the endogenous VLCFAs synthesis, in addition to a restricted VLCFAs intake.[46,47] This diet normalizes or at least reduces to 50% the baseline plasma C26 level in more than 70% of patients. However, it does not alter the rate of the progression of the disease once overt neurologic symptoms develop. Nevertheless, promising positive results in asymptomatic individuals have been reported, suggesting that increased VLCFAs are of pathogenic significance.[48] Additionally, peripheral nerve conduction velocities improve, parallel to the decreased plasma VLCFAs.[49] In a large clinical trial using GTE/GTO therapy in asymptomatic phenotypes with biochemical defect of X-ALD, 53 out of 61 persons remained normal for a period ranging from 3 months to 4 years. However, the analysis of such studies is very complex, since more than 50% of the asymptomatic persons with the biochemical defect escape the severe form of X-ALD, even without therapy.[5,19]

Bone marrow transplantation (BMT) was first employed in a 12-year-old boy with symptomatic X-ALD in 1984, resulting in substantial reduction of plasma VLCFAs level. In spite of these encouraging results, the patient's neurologic disabilities continued to advance.[50] Interest in BMT was rekindled by the report of Aubourg et al in 1990, of an 8-year-old boy

with mild neurological symptoms. After BMT, plasma VLCFAs level, brain MRI, neurologic examination, and psychometric function returned to normal.[51] BMT must be considered very early in an asymptomatic child with signs of demyelination on MRI, if a suitable donor is available.[52] Since inflammatory/immune changes appear to be of central importance in the pathogenesis of the demyelinating process, several therapeutic approaches have been tried to modify this mechanism. Immunosuppression with cyclophosphamide was not successful.[53,54] Intravenous immunoglobulin was reported to be helpful in some patients, but without clear benefit to others.[19,55,56] Pentoxifylline, a methylxanthine that inhibits the activity of tumor necrosis factor α (TNFα),[5,57,58] an important component in the X-ALD inflammatory response,[59] has been recently used in the treatment of X-ALD.

Diet low in VLCFAs and Lorenzo's oil were tried in all patients in this report and pentoxifylline in 2, without clinical improvement. The unavailability of HLA-matched donors precluded the use of BMT in our patients.

Other disappointing attempted therapeutic trials were plasma exchange,[60] and administration of oral carnitine or clofibrate.[45] Experimental work in animals includes transplantation of myelin-producing cells from healthy donors to the diseased ones.

Prenatal diagnosis with option of therapeutic abortion may be an alternative choice in affected families. The recent isolation of the X-ALD gene raises the hope of gene therapy in the future, but no clinical trials are in sight. Nevertheless, at present genetic counseling for the immediate and extended family members who may be at risk is an indispensable part of the management plan, and the importance of this preventive effort cannot be overemphasized.

In conclusion, X-ALD has been reported from different parts of the world; however, the existence of this lethal disease in Saudi Arabia, was not reported. The disease is more common than had been previously recognized, probably due to phenotypic variability and a wide spectrum of presentations, ranging from a rapidly fatal neurological disorder in early childhood to a slowly progressive paraparesis in the young adult. This report describes various aspects of this disorder in 10 patients and emphasizes the importance of early identification and treatment of asymptomatic but biochemically affected individuals, since all current therapeutic approaches are disappointing if overt neurological abnormalities have been already developed. Nevertheless, when the disease is diagnosed late, different modalities of treatment may still be offered through a comprehensive management program. The ethnography of Saudi Arabia and the fact that 6 of the 10 families studied in this report had at least one other male member affected by the disease, suggests that the incidence of X-ALD in Saudi Arabia may actually be higher than our experience at KFSH & RC.

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