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Signs of testicular insufficiency in adrenomyeloneuropathy and neurologically asymptomatic X-linked adrenoleukodystrophy: a retrospective study*

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Summary

X-linked adrenoleukodystrophy (X-ALD) is characterized by central nervous system demyelination, and impaired steroidogenesis in the adrenal cortex and testis. Most patients develop adrenocortical insufficiency. We studied retrospectively the frequency and severity of testicular dysfunction in 26 men with X-ALD. Twenty-one had adrenomyeloneuropathy and five patients were neurologically asymptomatic. In addition to obtaining a routine history and physical examination, we studied plasma levels of testosterone, sex hormone binding globulin, the free androgen index, and the plasma concentrations of dehydroepiandrosterone-sulphate, LH and FSH. In a subset of patients, the testosterone response to hCG and the LH and FSH responses to GnRH were also determined. Clinical signs of gonadal dysfunction were manifested by diminished libido (46%), largely overlapping with erectile dysfunction (58%), and failure of the testes to descend (15%). Physical examination revealed diminished body sexual hair (50%), gynaecomastia (35%), and small testes (12%). Laboratory studies showed low plasma total testosterone levels in 12%, and an insufficient increase after stimulation with hCG in 88% (15 of 17 patients tested). Plasma LH concentration was increased in 16%, and the plasma FSH level was elevated in 32%. The response of LH concentrations to GnRH stimulation was abnormally high in 47% (nine of 19 patients studied), and the response of FSH levels was too low in 16% (three of 19 patients tested). In conclusion, in a retrospective study of 26 men' with X-ALD, in 20 some signs of clinical hypogonadism were found. Plasma testosterone values were generally in the normal range, but upon testing of the hypothalamo-pituitary-testis axis some abnormalities became apparent.

Keywords: hypogonadism, hypothalamo-pituitary-testis axis, testis function, X-linked adrenoleukodystrophy

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Introduction

X-linked adrenoleukodystrophy (X-ALD) is an inherited disorder of peroxisomal metabolism, affecting at least one in 100 000 newborn males (Sereni *et al.*, 1993; van Geel *et al.*, 1994; Moser *et al.*, 1995). Biochemically, X-ALD is characterized by deficient degradation of saturated very long-chain fatty acids (VLCFAs) (Moser *et al.*, 1995), and elevated levels of these fatty acids can be demonstrated in plasma (Moser *et al.*, 1981) and fibroblasts (Moser *et al.*, 1980). Accumulation of VLCFAs is associated with demyelination of the nervous system, and impairment of steroid hormone synthesis in the adrenal cortex and the testis. The phenotypic expression of X-ALD is highly variable, even in patients with identical mutations in the X-ALD gene (Ligtenberg *et al.*, 1995). The two most frequent phenotypes are childhood cerebral ALD (CCALD) and adrenomyeloneuropathy (AMN) (van Geel *et al.*, 1994; Moser *et al.*, 1995). The onset of CCALD is between 5 and 10 years of age, and is characterized by a very rapidly progressive cerebral demyelination. Patients with AMN manifest a slowly progressive myeloneuropathy, with an onset in the second or third decade.

The severe inflammatory reaction that causes demyelination within the central nervous system argues for the involvement of the immune system in X-ALD (Griffin *et al.*, 1985; Powers *et al.*, 1992). Glucocorticoids and sex steroids are involved in the functioning of the immune system (Grossman, 1994; Chrousos, 1995).

Steroid hormone production in adrenocortical cells and testicular Leydig cells may be impaired by at least three mechanisms: (1) VLCFA-cholesterol esters accumulate intracellularly, and are ultrastructurally visible as lamellar inclusions (Powers & Schaumburg, 1974); (2) VLCFA-cholesterol esters are poor substrates for cholesterol-ester hydrolases (Powers, 1985), leading to a shortage of cholesterol, the precursor of steroid hormone synthesis; (3) membrane rigidity is increased by the incorporation of VLCFAs in cell membrane lipids, thus interfering with the receptor binding of ACTH, and possibly also of LH and FSH (Whitcomb *et al.*, 1988). As a result, hormone production by the adrenal cortex and the testis declines. In the testis, secondary to Leydig cell failure, Sertoli cell function, and consequently spermatogenesis, are impaired. Adrenocortical insufficiency may precede, accompany or follow the involvement of the nervous system (Moser *et al.*, 1991). Approximately 80% of X-ALD patients with neurological deficits suffer from Addison's disease. When adrenocortical insufficiency is the only clinical manifestation of X-ALD, this is known as the 'Addison-only' phenotype (Sadeghi-Nejad & Senior, 1990; Jorge *et al.*, 1994).

Whereas the adrenocortical dysfunction in X-ALD patients is well documented, the frequency and severity of testicular dysfunction have received much less attention (Griffin *et al.*, 1977; Powers & Schaumburg, 1980; Libber *et al.*, 1986; Moser *et al.*, 1991). We retrospectively studied 26 men with X-ALD: during clinical visits their histories were taken with regard to their gonadal function, while their hormonal reproductive status was also assessed.

Patients and methods

Patients

Twenty-six patients with a median age of 34 years (range 18–78) were studied (Table 1). In all patients, X-ALD had been demonstrated by elevated levels of hexacosanoic acid and an increased hexacosanoic/behenic acid (C26:0/C22:0) ratio in plasma (Moser *et al.*, 1981). Twenty-one patients had AMN, the median duration of neurological symptoms being 6 years (range < 1–30). Four had the biochemical defect of X-ALD, but neither neurological abnormalities nor adrenocortical insufficiency (asymptomatic ALD). One patient (Z) – a brother of a patient with AMN (patient Y) and thus tested – was neurologically asymptomatic, but manifested primary testicular, adrenocortical and thyroidal failure, which previously had been attributed to a polyglandular autoimmune syndrome.

Fourteen patients received hydrocortisone substitution therapy, which was combined with fluorhydrocortisone in six cases. The median duration of treatment for adrenocortical insufficiency was 6 years (range < 1–33). Patients F, J, U and V were referred to us from other hospitals, and had already been treated for several months with 'Lorenzo's oil', an experimental dietary supplement of monounsaturated fatty acids, which aims at the reduction of VLCFA biosynthesis (Odone & Odone, 1989; Rizzo *et al.*, 1989).

History taking and physical examination

Patients gave their informed consent to inclusion in the study upon their follow-up visits. The retrospective analysis was approved by the hospital ethical review board. Retrospective information was obtained about testicular descent, age at the onset of puberty, libido, erectile function and involuntary infertility, on the basis of a routine clinical history taking. No standardized questionnaires were used.

Besides a general physical examination, sexual hair growth and the position and volume of the testes were noted. Testicular volumes were assessed on the basis of clinical judgment. Normal testicular volume in adult Caucasians is >17 mL (Zachmann *et al.*, 1974).

Laboratory investigations

In plasma, basal levels of total testosterone were measured with an in-house RIA, without extraction and chromatography, and with tritiated testosterone as a label. Reference values for men ranged from 11.0 to 35.0 nmol/L in our laboratory [interassay coefficient of variation (ICV): 11.3%]. Levels of sex hormone binding globulin (SHBG) were

Table 1. Description of patients, history and physical examination

Patient	Age (years)	Phenotype of X-ALD	Duration of myelo-and/ or neuro-pathy (years)	Treatment for adrenocortical insufficiency (years)	DHEA-S (μmol/L) (n = 2–10)	Libido	Erectile function	Sexual hair	Gynaecomastia
A	18	asympt ALD	–	–	0.9	+	+	↓	–
B	21	AMN	<1	–	2.1	+	+	↓	–
C	24	asympt ALD	–	–	3.7	+	+	↓	+
D	28	asympt ALD	–	–	2.1	+	+	+	–
E	30	AMN	1	–	6.25	↓	↓	↓	+
F	30	AMN	5	3	1.0	↓	–	?	–
G	31	asympt ALD	–	–	0.8	+	↓	↓	–
H	31	AMN	<1	3	0.9	+	+	↓	–
I	31	AMN	20	1	1.3	↓	–	↓	–
J	32	AMN	2	3	2.7	↓	+	↓	–
K	32	AMN	5	<1	0.4	+	↓	+	+
L	33	AMN	5	15	1.0	↓	↓	+	–
M	34	AMN	3	2	2.6	+	+	+	–
N	35	AMN	6	3	0.6	+	↓	+	+
O	36	AMN	5	–	0.5	↓	↓	+	+
P	36	AMN	6	14	2.1	+	↓	+	–
Q	41	AMN	30	19	3.1	↓	↓	↓	–
R	43	AMN	10	6	0.4	–	–	+	–
S	43	AMN	10	6	0.85	↓	↓	↓	–
T	44	AMN	9	–	1.7	+	+	+	+
U	45	AMN	3	–	0.8	+	+	↓	–
V	48	AMN	15	6	0.6	+	↓	+	+
W	53	AMN	20	–	1.2	↓	+	↓	+
X	54	AMN	25	–	2.1	–	–	+	–
Y	74	AMN	18	–	0.6	+	+	↓	–
Z	78	PAS	–	33	<0.1	–	–	↓	+

+ present; – absent; ↓ diminished; AMN = adrenomyeloneuropathy; Asymptomatic ALD = patient with elevated plasma VLCFAs, and normal neurological examination; PAS = polyglandular autoimmune syndrome.

measured using an immunoradiometric assay (Farmos Diagnostica, Turku, Finland). Reference values ranged from 12 to 75 nmol/L (ICV: 9.1%). The free androgen index (FAI) was calculated according to the formula (testosterone/ SHBG) × 100%. Reference values ranged from 20 to 90. LH and FSH concentrations in plasma were measured using a commercial RIA (Amerlex M, Kodak Clinical Diagnostics Ltd, Amersham, UK). Basal LH concentrations in healthy men ranged from 5 to 15 U/L (ICV: 4.5%), and basal FSH concentrations ranged from 1 to 10 U/L (ICV: 11.3%).

Plasma testosterone levels were also measured in 17 patients ≈48 h after i.m. injection of 1500 IU hCG (Pregnyl; Organon, Oss, the Netherlands). In our laboratory a normal response is defined as an increase in the level of testosterone of at least 150% over baseline values (Behre *et al.*, 1996). The concentrations of LH and FSH in plasma were determined in 19 patients 15 min before to 120 min after i.v. administration of 100 μg GnRH (Relefact; Hoechst, Amsterdam, the Netherlands). In our laboratory a normal response of LH is defined as an increase in the basal level of LH between 200% and 500%, and a normal response of FSH as an increase of at least 50% of the basal FSH level (Behre *et al.*, 1996).

In addition, we studied the plasma levels of progesterone, androstenedione and dehydroepiandrosterone-sulphate (DHEA-S). Plasma concentrations of progesterone were measured by coated tube RIA (Orion Diagnostica, Espoo, Finland). In our laboratory, levels in healthy men vary from 1.0 to 3.0 nmol/L (ICV: 7.1%). Plasma androstenedione was determined after diethylether extraction with ^{125}I coated tube RIA (Diagnostic Products Corporation, Los Angeles, CA, USA). In our laboratory, reference values ranged from 1.0 to 10.0 nmol/L for men (ICV: 13%).

The plasma level of the androgen precursor DHEA-S was measured using a commercial RIA (Coat-a-count, Diagnos-

tics Products Corporation, Los Angeles, CA, USA). Reference values in men vary from 2 to 10 mmol/L in our laboratory (ICV: 6–9%).

Results

Patient history

In four of the 26 subjects (15%), one of the testes had failed to descend (Table 1). In all patients puberty had occurred before the age of 15 years. Twelve out of 26 men (46%) experienced absent or diminished libido largely overlapping with 15 of 26 patients (58%) who disclosed that their erectile function was diminished or absent. Two of the 26 men (8%) had been referred for assisted reproduction.

Physical examination

All patients manifested a typical pattern of baldness, i.e. soft and scant scalp hair. This type of balding is distinctly different from alopecia androgenica. In 15 of the 26 men (58%) the pubic hair pattern was female, and in 13 of the 26 patients (50%) body hair was sparse. Gynaecomastia was present in nine of the 26 patients (35%). In three of 26 patients (12%), testicular volume was <17 mL. In 20 of the 26 patients at least one of the above symptoms was encountered.

Laboratory studies

The basal plasma concentration of testosterone was below the lower limit of normal of 11 nmol/L in three of 26 patients (12%; Table 2). SHBG was within normal limits in all patients, and the FAI was abnormally low in one of

Table 2. Plasma steroid and pituitary hormone concentrations

Patient	Total testosterone (nmol/L)	Testosterone increase after hCG (%)	Basal LH (IU/L)	LH increase after GnRH (%)	Basal FSH (IU/L)	FSH increase after GnRH (%)
A	18.1	nm	7.5	nm	4.0	nm
B	16.4	nm	9.0	nm	**15.5**	nm
C	24.0	**54**	7.8	400	6.3	59
D	19.5	**91**	7.8	310	5.3	240
E	13.7	**53**	7.0	**543**	6.3	91
F	18.4	nm	7.5	nm	4.0	nm
G	23.5	**5**	7.0	**643**	5.8	81
H	23.0	**59**	6.5	**776**	5.0	70
I	24.0	nm	9.0	nm	**11.0**	nm
J	15.6	nm	**24.0**	nm	9.0	nm
K	17.7	**46**	**25.5**	268	**10.5**	52
L	17.8	**74**	9.8	241	5.1	53
M	15.6	nm	3.8	**557**	3.5	**43**
N	15.5	nm	**24.0**	283	**28.0**	50
O	12.8	111	10.5	**852**	**32.5**	115
P	19.2	**61**	5.7	**1391**	9.0	156
Q	17.9	**23**	8.3	357	5.5	91
R	12.4	126	10.3	**531**	10.0	83
S	**10.8**	**9**	9.5	326	5.8	**45**
T	13.3	**72**	7.5	473	**13.5**	56
U	17.9	**51**	9.5	236	4.0	**38**
V	14.7	**37**	8.3	334	5.0	50
W	16.0	**69**	8.5	641	**21.0**	91
X	**9.8**	**57**	7.0	671	10.0	60
Y	14.7	nm	nm	nm	nm	nm
Z	**5.3**	nm	**51.0**	nm	**49.0**	nm
median	16.2	57	8.3	473	6.3	59
normal	11–35	>100	5–15	200–500	1–10	>50

Bold typeface = abnormal; nm = not measured.

the 26 patients (4%). Testosterone increase after i.m. injection of hCG was judged insufficient in 15 of 17 men tested (88%).

The basal LH level was elevated in four of 25 patients (16%), and basal FSH was elevated in eight of 25 (32%). The LH increase was abnormally high in nine of 19 patients (47%), and FSH increase after GnRH administration was diminished in three of 19 patients (16%).

Plasma progesterone levels were <1.0 nmol/L in 10 of 13 men (78%). Plasma levels of androstenedione ranged between 1.0 and 9.9 nmol/L, with a median value of 2.6 nmol/L, and was within normal limits in all of the 14 patients tested.

The plasma DHEA-S concentration varied from 0.1 to 6.25 mmol/L, and was below the lower limit of normal of 2 mmol/L in 15 of 24 patients (63%).

Discussion

In our routine history taking we focused our attention on clinical symptoms of impaired testicular steroidogenesis in adult patients with X-ALD. Though ultrastructural lesions, characteristic for X-ALD, can already be demonstrated in the fetal testis (Powers *et al.*, 1982), exact data on gonadal function in boys and men with X-ALD are still sparse. This is in part due to the difficulty of diagnosing testicular insufficiency in prepubertal boys, in whom testicular abnormalities do not become apparent due to very low prepubertal gonadotrophin levels. Libber *et al.* (1986) found normal plasma testosterone but elevated LH and FSH concentrations in three of seven X-ALD patients, compatible with partial primary testicular insufficiency. Powers & Schaumburg (1980) reported impaired sexual function as the first symptom of AMN in five of six men. Moser *et al.* (1991) found testosterone levels at the lower level of normal in 22% of 69 AMN patients, probably on the basis of primary testicular failure, as indicated by increased plasma levels of LH in 42%, and elevated FSH concentrations in 30%. However, a combination of primary and secondary gonadal failure due to hypothalamic-pituitary dysfunction also has been reported (Peckham *et al.*, 1982).

Interestingly, signs and symptoms of testicular dysfunction were found in the four patients (A, C, D and G) with neither neurological symptoms nor Addison's disease. They had been identified by family screening. It is known that adrenocortical insufficiency in X-ALD may precede, accompany or follow the onset of neurological symptoms, just as we found in our patients (Table 1); some patients with isolated adrenocortical insufficiency (the 'Addison-only' phenotype) may even remain free of neurological involvement well into their sixties (Moser *et al.*, 1991). So, in analogy to the adrenocortical dysfunction, symptoms of testicular insufficiency may precede the neurological abnormalities. We propose to phenotype these subjects 'gonadal insufficiency-only' patients.

We found an undescended testis in four of our patients (15%), which is much higher than the normal frequency of 0.8% (Couz-Palais, 1966). These four men (patients B, N, O and W) had clearly elevated basal FSH levels. The non-descent of the testes may reflect testicular damage already present during fetal life, as it is now believed that the testis itself plays an endocrinological role in its descent (Hutson & Donahoe, 1986). The onset of puberty, primarily a hypothalamic-pituitary function, was not delayed in any of our patients. Clinically, gonadal dysfunction was manifested by diminished or absent erectile function in 58% of our patients and loss of libido in 46%. Two patients were referred for assisted reproduction. Androgen deficiency was further suggested by a female pubic hair pattern in 58% of the patients, sparse body hair in 50%, and gynaecomastia in 35%. So, in 20 of 26 patients at least one clinical sign of hypogonadism was encountered.

The sparsely implanted scalp hair present in all patients differed in its appearance from alopecia androgenica. We assume this is related to the alopecia seen in autoimmune disorders, and not a result of testicular insufficiency. Dumic *et al.* (1992) reported identical scalp hair pattern in two female carriers. At least three patients (D, I and Z) reported that the characteristic sparse scalp hair had already manifested itself before puberty. In fact, in the very first report of a patient with AMN, first areolar, then diffuse alopecia was noted from the age of 8 years: a skin biopsy revealed chronic inflammatory infiltrates in the corium (Budka *et al.*, 1976). Additionally, the coexistence of X-ALD and autoimmune endocrine disease has been reported in several patients (Federico *et al.*, 1988; Dumic *et al.*, 1992). Similarly, in patient Z the biochemical defect of X-ALD and an autoimmune polyglandular syndrome were intertwined.

The primary sexual characteristics (in particular testicular volume) were within the normal limits in most patients. However, once the primary sexual characteristics have been established by normal androgen levels, they can subsequently be maintained by relatively low levels of androgens (Braunstein, 1991). We found basal plasma testosterone levels below reference values in only 12% of our patients, which contrasts with the prevalence of clinical hypogonadism. But upon testing of the hypothalamo-pituitary-testis axis in 88% of the men, the testosterone increase after hCG stimulation was subnormal, reflecting deficient testicular steroidogenesis, and/or deficient gonadotrophin receptor function. This was further corroborated by elevated basal LH levels in 16% of our patients, and an exaggerated response to GnRH in 47%. Moreover, a sensitive endocrine parameter of the quality of spermatogenesis, the plasma FSH concentration (Bergmann *et al.*, 1994), was increased in 32% of the X-ALD patients. Analogous to the increase in ACTH secretion to maintain adequate cortisol production, elevated gonadotrophin levels might strive to preserve normal testicular function. In patients M, S and U, with their diminished FSH response after stimulation, an additional

hypothalamic dysfunction may exist. Plasma levels of the testosterone precursor progesterone were also low, suggesting that the impairment in steroidogenesis may be localized at a step earlier in the cascade of steroid synthesis. We admit that our endocrine testing of the hypothalamo-pituitary-testis axis has been less than ideal, but we believe there is reason to pay more attention to testicular (dys)function in patients with X-ALD. Further, it is theoretically possible that the clinical hypogonadism of the patients, in the presence of fairly normal testosterone levels, may be explained by the accumulation of VLCFAs in the cell hampering testosterone receptor and postreceptor events.

Some of the patients might benefit from androgen replacement. In endocrine substitution therapy, androgens are sometimes unduly overlooked. Androgens play a role not only in (the libidinous aspects of) sexuality, but also in the preservation of bone and muscle mass, and mood and substitution therapy may add to the quality of life (Wang *et al.*, 1996). So far, androgen administration has not been part of our treatment of X-ALD, since we had some expectations of the beneficial effects of dietary treatment on adrenal cortex and testicular function. However, treatment with 'Lorenzo's oil' does not improve adrenocortical or testicular function; increasing plasma levels of FSH during treatment may even reflect ongoing deterioration of testicular function (Assies *et al.*, 1994). A consideration in this study is that patients with X-ALD suffer from a debilitating disease. It is known that poor physical health may have a suppressive effect on the hypothalamo-pituitary-testis axis resulting in decreased testosterone production. Yet, in three of the four asymptomatic X-ALD patients the testosterone response to hCG stimulation was subnormal. Erectile dysfunction in these patients with AMN could be due to myeloneuropathy. However, erectile function was also impaired in one asymptomatic patient while seven patients with myeloneuropathy had normal erectile function.

Finally, the immune system is involved in the process of demyelination within the central nervous system in X-ALD (Griffin *et al.*, 1985; Powers *et al.*, 1992). The importance of corticosteroids in regulating virtually every component of the immune and inflammatory response has long been appreciated (Chrousos, 1995), and a significant role of sex steroids in the immune system is also emerging (Grossman, 1994). Further evidence is accumulating for a distinct role of the (sex) steroid precursor DHEA-S in the regulation of immune responses (Padgett & Loria, 1994). Indeed, we found plasma DHEA-S levels below the lower limit of 2 mmol/L in 63% of adult men with different variants of X-ALD. The low plasma DHEA-S levels were not the result of exogenous glucocorticoid administration. They were also present in patients without glucocorticoid administration, even in asymptomatic patients. We hypothesize that adrenal steroids, their precursors and metabolites may be involved in the variable phenotypic expression of X-ALD via their influence on the immune system.

In conclusion, in our retrospective analysis of testicular function in adult men with X-ALD, we found clinical signs and symptoms of hypogonadism in no less than 20 of the 26 (77%) patients, sometimes in the absence of neurological deficits, adrenocortical dysfunction, or both. Basal plasma testosterone levels were generally in the normal range, but testing of the hypothalamo-pituitary-testis axis indicated abnormalities in many cases. Overt or subclinical testicular insufficiency may even be the only manifestation of X-ALD. We recognize the methodological weakness of our retrospective assessment of male reproductive and sexual function. However, we feel that our data prompt the evaluation of testis function in X-ALD, and that this disorder should be included in the differential diagnosis of primary hypogonadism of unknown aetiology.

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