OPHTHALMOLOGIC AND SYSTEMIC FEATURES OF THE ALSTRÖM SYNDROME: REPORT OF 9 CASES

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SUMMARY

The Alström syndrome is a rare autosomal recessive disorder characterized by pigmentary retinopathy, diabetes mellitus, sensorineural deafness and obesity. A normal intelligence is often present.

We report 9 patients.

RÉSUMÉ

Le syndrome d'Alström est une maladie rare, autosomale et récessive. Elle est caractérisée par une rétinite pigmentaire, un diabète et une surdité perceptive. Des enfants souffrants de cette maladie sont fréquemment obèses et ont le plus souvent une intelligence normale.

Nous rapportons 9 patients avec le syndrome.

SAMENVATTING

Het syndroom van Alström is een zeldzame autosomale recessieve aandoening die wordt gekenmerkt door de aanwezigheid van retinitis pigmentosa, diabetes mellitus, perceptiedoofheid, overgewicht en in de meeste gevallen een normale intelligentie. Wij stellen 9 patiënten voor met deze aandoening.

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KEY-WORDS

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MOTS-CLÉS

syndrome d'Alström
acanthosis nigricans
obésité
cardiomyopathie
surdité perceptive
rétinite pigmentaire

INTRODUCTION

In 1959 Alström et al *(1)* described 3 patients with atypical pigmentary retinopathy, sensorineural deafness, obesity, diabetes mellitus and normal intelligence.

Klein and Ammann *(6)* and Goldstein and Fialkow *(5)* added other features to the Alström syndrome: acanthosis nigricans, male hypogonadism, renal disease, baldness and hypertriglyceridemia. Dilated cardiomyopathy, hepatic degeneration and growth hormone deficiency are presently recognized to be other signs of the syndrome *(10)*.

We present 9 patiens with this rare disease. Our aim is to discuss the ocular and systemic manifestations of this syndrome in our patients.

We want to emphasize that the diagnosis of Alström's syndrome is often difficult, because not all cardinal features appear initially.

PATIENTS AND METHODS

Seven patients with Alström syndrome were examined in 1995-2000. Two other patients, who

Fig. 1: Pigmentary retinopathy with waxy optic disc and narrow vessels without bone spiculae

died, were added to this report using a retrospective review of case notes.

Case reports

Table 1 shows the ophthalmologic features of the Alström syndrome.
In our case series 8 of 9 patients had searching nystagmus since the age of 3 months. Photophobia was present in all patients. Severe visual impairment manifested itself before the age of 3 years. The fundus of all our patients showed a pale optic disc and narrowing of the retinal vessels, without bone spiculae (figure 1). An ERG was performed in all patients. The ERG was nondetectable in 4 of 9 patients. In 5 of 9 patients a cone-rod dystrophy was present.

Table 2 shows the systemic features of the syndrome.
Eight patients had an acquired sensorineural hearing loss. In 3 patients the onset of the hearing loss was in the first decade, while in 5 patients the hearing loss was detected in the second decade. Audiometry was repeated and showed progression of the hearing loss (figure 4). Seven patients had a body mass index of more than 25kg/m^2. One patient (P9) with a body mass index below 25, showed a weight above the 90th percentile at the age of 5 and a height below the 3th percentile. Her sister (P4) had a normal body mass index and no obesity (weight 50th percentile) but a short stature (below 3th percentile).
Only 2 of 9 patients had proven type 2 diabetes mellitus by a glucose tolerance test. Acanthosis nigricans, a skin lesion characterized by velvety hyperpigmented patches in intertriginous areas, (figure 2) was found in 3 patients. Three patients had a normal intelligence, the others had mild mental retardation. This was caused in one patient (P4) by birth asphyxia.

Table 3 shows the additional systemic features.
One male patient had small testicles, with normal secondary sex characteristics. Three patients had increased serum creatinine levels. One patient (P1) had end stage renal disease and required hemodialysis. In 3 patients liver function tests were abnormal: raised gamma glutamyl transpeptidase, alanine aminotransferase and aspartate aminotransferase were found in two patients. Hypertriglyceridemia was present in two patients, one patient showed also hypercholesterolemia. Scoliosis was found in 3 patients (figure 3).
Three patients had gone through an episode of infantile dilated cardiomyopathy. Two of them

Fig. 2: Acanthosis nigricans in the axillary region (P7)

Table 1: *Ophthalmologic Features*

	P1	P2	P3	P4	P5	P6	P7	P8	P9
birth year	1960	1973	1982	1983	1984	1987	1988	1988	1995
sex	F	M	F	F	F	M	F	M	F
searching nystagmus	+	+	+	+	+	NM	+	+	+
photophobia	+	+	+	+	+	+	+	+	+
visual acuity									
first exam	1/10 (10y)	1/10 (8y)	2/10 (2y)	1/20 (5y)	1/10 (5y)	1/10 (3y)	< 1/20 (4y)	1/10 (2y)	1/20 (3y)
last exam	< 1/20 (23y)	LP (11y)	< 1/20 (14y)	LP (17y)	LP (14y)	1/10 (11y)	LP (8y)	1/20 (9y)	
pigmentary retinopathy	+	+	+	+	+	+	+	+	+
ERG									
non detectable			+ (8y)		+(3y)		+(4y)	+(6y)	
cone-rod dystrophy	+ (4y)	+ (6y)		+ (13y)		+ (8y)			+ (2y)

Legend
NM: non mentioned
P4 and P9 are sisters

Table 2: *Systemic Features*

	P1	P2	P3	P4	P5	P6	P7	P8	P9
birth year	1960	1973	1982	1983	1984	1987	1988	1988	1995
sex	F	M	F	F	F	M	F	M	F
sensori-neural									
hearing loss (dB)	+	+	+	+	+	–	+	+	+
first exam	NM (12y)	NM (15y)	20dB (12y)	NM (12y)	35dB (12y)		NM (8y)	30dB (5y)	NM (5y)
last exam	70dB (25y)		40dB (16y)		NM (14y)			60dB (9y)	
body mass index $> 25 kg/m^2$	+	+	+	–	+	+	+	+	–
diabetes mellitus	+	–	–	–	–	+	–	–	–
acanthosis nigricans	–	–	–	–	–	+	+	+	–
intelligence									
normal			+		+				+
mild MR (IQ 50-70)	+	+		+		+	+	+	

Legend
NM: decibels non mentioned

Table 3: *Additional Systemic Features*

	P1	P2	P3	P4	P5	P6	P7	P8	P9
birth year	1960	1973	1982	1983	1984	1987	1988	1988	1995
sex	F	M	F	F	F	M	F	M	F
male hypergonadotrophic hypogonadism		+				–		–	
renal impairment	+	+	–	–	–	+	–	–	–
hepatic disease	+	+	–	–	–	+	–	–	–
hypertriglyceridemia	+		–	–	–	+	–	–	–
scoliosis	–	–	+	+	–	–	+	–	
infantile dilated cardiomyopathy	+	+	+	–	–	–	–	–	–
deceased	30y	20y							

(P1, P2) died of cardiac arrest at the age of respectively 20 and 30 years. Consanguinity was present in the families of two patients (P6, P8). Karyotype analysis was normal in all patients.

DISCUSSION

Alström syndrome is a rare autosomal recessive disease *(10)*. Less than 80 patients are reported in the world literature since 1959. A diagnostic test in a suspected case of Alström

syndrome is not yet possible. The locus of the gene has been identified (2p13) by linkage analysis but the gene has not been cloned *(3)*.
In our case series all patients presented initially searching nystagmus (except P6) and photophobia. Impairment of vision manifested itself during the first year of life. In the 1st decade, the visual acuity was 1/10 or less and in 4 patients the visual acuity decreased to light perception in the second decade. In the first decade optic atrophy and narrowing of the vessels without bone spiculae were seen. Later in the disease chorioretinal atrophy and large clumps of pigment develop. The ERG in Alström syndrome demonstrates an early cone dysfunction followed by a rapid deterioration of the rod responses *(10, 13)*. Our patients had either a severe cone-rod dysfunction or a non recodable ERG.
The second cardinal feature of Alström syndrome is the progressive sensorineural deafness *(1, 9, 10)* in the first decade.
The hearing loss is usually detected during a screening audiometry at the end of the first decade and is progressive (fig 4). The audiometry of P8 shows a perceptive hearing loss of 20-30dB in 1993. Four years later, a progression of the hearing loss is noticed (60dB).
Childhood-onset obesity *(1, 9, 10)* is the third cardinal feature. Seven patients had a body mass index of more than 25. The two other patients had truncal obesity and short stature but a body mass index below 25. There was no growth hormone deficiency in these two patients. Growth retardation in AS patients is preceeded by an advanced bone age in adolescence *(7).*
Maturity onset diabetes mellitus *(1, 9, 10)* with insulin resistance is a fourth feature and usually develops in the second or third decade. Only 2 of 9 patients had diabetes so far. Hyperinsulinemia was not yet present in the other 7 patients. Acanthosis nigricans is a frequently associated finding in youths with diabetes mellitus *(10)*. Of our 3 patients with acanthosis nigricans one patient had also type 2 diabetes mellitus (P6). .
Normal mental development is the fifth cardinal feature of the Alström syndrome *(1, 9, 10)*. An assessment with the "Wechsler Intelligence Scale of Children revised" (WISCR) was performed. Three patients had a normal intelligence, while the others showed a mild mental retardation. One child had a mild mental retardation caused by birth asphyxia (P4).

Fig. 3: Two sisters with the syndrome (P4 and P9), notice the obesity of both and thoracic scoliosis in the older girl

There are several additional features of Alström syndrome. Hypergonadotrophic hypogonadism *(6, 9)* is a variable feature. No patient with Alström syndrome has ever been known to reproduce *(9).* One of three males in our series had small testicles but was normally virilized. Renal disease is a common and late appearing sign of Alström syndrome *(5, 9, 10)*. It is an important cause of death. Three patients in our series had renal dysfunction. One patient with renal failure at the age of 30 years required hemodialysis and died a few months later of cardiac arrest (P1).
Hepatic dysfunction has also been reported in the Alström syndrome *(2, 10)* and was suggested to be related to alcoholism *(12)*. In our

Figure 4A: audiometry P8 (1993)

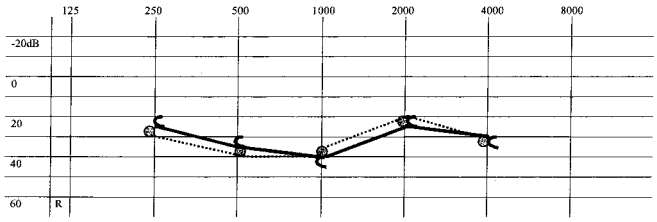


Figure 4B: audiometry P8 (1996)

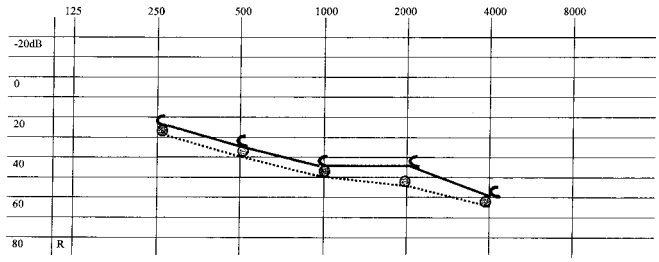
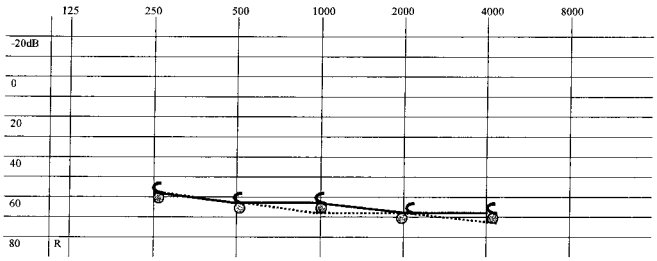


Figure 4C: audiometry P8 (1997)



Sound transmission : air

Sound transmission : bone

Figure 4: Progressive sensorineural deafness

series the patients with renal disease had also elevated liver enzymes. Echography of the liver showed steatosis in one patient (P1) who had also hyperlipidemia. Lipid abnormalities are a variable feature *(5, 9, 10)*. They can be an intrinsic feature or can be related to the obesity and diabetes mellitus *(9)*. Two of our patients had hypertriglyceridemia and one also hypercholesterolemia. They both had diabetes mellitus (P1, P6). Skeletal anomalies are also present in Alström syndrome *(9)*. Three patients developed thoracic scoliosis.

A dilated cardiomyopathy can be an early sign of Alström syndrome *(8)*. In 1989 Russell-Eggitt et al mentioned the association of Leber's congenital amaurosis with cardiomyopathy as a separate entity *(11)*. On follow-up these patients were found to develop the Alström syndrome. Three of our patients between the age of 2-4 months experienced a transient episode of cardiomyopathy. Echocardiography showed a left ventricular dilatation. They were treated with digoxin. Endocardial biopsy was performed in two cases and showed fibro-elastosis cordis (P1, P2). These two patients died of cardiac arrest at the age of 20 and 30 years. They both had additional risk factors. They suffered from hepatic and renal disease and one patient had diabetes mellitus.

With this report we want to emphazise that making the diagnosis of the Alstöm syndrome is difficult because not all cardinal features appear initially and there are some similarities with the Bardet-Biedl syndrome (BBS). The visual acuity in children with the BBS is usually not less than 6/36 at the age of 10 years *(10)*. Progressive sensorineural deafness is not a major feature in BBS *(4, 10)*. Childhood-onset obesity is also present. Type II diabetes mellitus is relatively uncommon and acanthosis nigricans is rare *(4, 10)*. Mental retardation is a variable feature. Polydactyly is present in the Bardet-Biedl Syndrome.

It is important to recognize the early manifestation of the Alström syndrome: cone-rod dystrophy, dilated cardiomyopathy and obesity *(8)*. Early diagnosis improves medical and educational support.

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