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## Multi-system signs and symptoms in X-linked ataxia carriers

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### Abstract

Neurological, auditory, vestibular and ocular motor examinations were performed on 3 definite and 3 possible heterozygous carriers of a previously described X-linked multi-system disorder with early childhood onset, rapid progression and a fatal outcome (Arts et al., 1993). The symptoms, i.e., delayed motor development, ataxia, hearing loss and subnormal intelligence, were so evident in 2 of the possible carriers that they could be redesignated as probable carriers. Other symptoms in the definite and probable carriers were clubfeet, dysarthria, intention tremor and abnormal gait, while their signs included dysdiadochokinesia, ataxic paraplegia, abnormal muscle tendon reflexes and extensor plantar responses. All the symptomatic carriers developed moderate-to-severe sensorineural hearing loss with normal stapedial reflexes and brain stem auditory evoked potentials (BAEPs) in those in whom this could be evaluated. Speech discrimination was disproportionately poor unilaterally in one case from whom no BAEPs could be obtained because of her degree of hearing loss. Various combinations were found of high gain of the vestibulo-ocular reflex, spontaneous nystagmus and directional preponderance of vestibularly evoked nystagmus, slowing, hypometria or multi-stepping of saccades, saccadic intrusions of eye movements (macro square wave jerks, double saccadic pulses), impairment of smooth pursuit eye movements and optokinetic nystagmus, and failure of visual fixation suppression of vestibularly evoked nystagmus. Such findings indicate major involvement of the (vestibulo)cerebellum and the vermis. MRI in one carrier showed mild cerebellar atrophy.

**Keywords:** Sensorineural hearing loss; Speech discrimination; Brain stem auditory evoked potential; Vestibular system; Saccades; Smooth pursuit eye movement; Manifesting heterozygote

### 1. Introduction

X-linked multi-system disorders are rare. Recently a disorder with an early onset has been described that affected at least the posterior columns, peripheral motor and sensory neurons, the cranial nerves and/or nuclei; this resulted in ataxia, muscle weakness, deafness and visual impairment (Arts et al., 1993). Recurring infections were the cause of death in all the cases before the age of 5 years, except for one. Autopsy in one case revealed a normal brain but almost complete absence of myelinated fibres in the dorsal columns (only) of the spinal cord. Some carriers showed hearing loss. These and other signs and symptoms were only mentioned briefly in a previous report. The present report elaborates on the signs and symptoms of some of the carrier females in whom we evaluated the auditory, ocular motor and vestibular responses.

### 2. Clinical and genetic data

The pedigree showed 12 affected boys in three generations. Clinical data have already been presented elsewhere (Arts et al., 1993). In 2 out of the 3 affected boys, hearing loss combined with impairment of vision was definitely present. We were able to examine 3 definite (III.14, IV.15, IV.28, Arts et al., 1993, Fig. 1) and 3 possible heterozygous carriers (IV.43, IV.44, IV.45). The possible carriers IV.44 and IV.45 were redesignated as probable carriers because of their clinical symptoms (see below).

#### 2.1. Case reports

##### 2.1.1. Case 1 (definite carrier, IV.28), (Arts et al., 1993, Fig. 1)

This 32-year-old woman mentioned that her hearing loss had been confirmed at the age of 12 years. She had not walked until she was 5 years old and had been

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suffering from muscle stiffness from about that age. Her hearing loss was progressive; there was no history of otological infections or the use of ototoxic drugs. She was fitted with her first hearing aid at the age of 25 years. Neurological examination revealed dysarthria, dysdiadochokinesia, ataxic paraplegia, clubfeet, muscle tendon hyperreflexia and extensor plantar reflexes. She complained of dizziness, instability and frequent falls. MRI showed mild cerebellar atrophy.

According to this woman, her mother (III.10), who was 68 years old, had started to become deaf at about 35 years of age and showed a wide-based and ataxic gait.

#### 2.1.2. Case 2 (definite carrier IV.15)

This 42-year-old woman noticed progressive hearing loss at the age of 27 years. There was no history of otological infections or the use of any ototoxic drugs. She had some complaints of dizziness and according to her husband she walks like someone who is drunk. She showed dysdiadochokinesia and some broadening of gait but no other neurological signs; somatosensory evoked potentials (SSEPs) were normal.

#### 2.1.3. Case 3 (definite carrier III.14)

This 60-year-old woman was known to have generalized epilepsy without any other neurological or otological signs or symptoms. She was using sodium valproate 600 mg twice a day.

#### 2.1.4. Cases 4 and 5 (both probable carriers IV.44 and IV.45)

These are fraternal twins. Pregnancy and delivery were uneventful except for the use of phenobarbital by their mother because of epilepsy. Delayed motor development was present in both women. Patient IV.44 proved to have valvular pulmonary artery stenosis. At primary school, at the age of 6 years, hearing loss became evident in both girls. Neurological examination at 9 years of age revealed intention tremor, ataxic paraplegia, diminished muscle tendon reflexes and extensor plantar responses. Eye movements were normal in patient IV.45, but IV.44 showed gaze-evoked nystagmus to the left. At 23 years of age, both women showed ataxic paraplegia, hypotonia, diminished muscle tendon reflexes, dysdiadochokinesia, a positive rebound phenomenon and extensor plantar responses. Both patients had subnormal intelligence.

#### 2.1.5. Case 6 (possible carrier IV.43)

This 27-year-old woman had no neurological or otological signs or symptoms. She had normal intelligence and a young healthy daughter.

### 3. Methods

#### 3.1. Auditory system

Pure-tone audiograms were obtained in a sound treated room with an Interacoustics AC5 audiometer (Interacous-

tics, Assens, Denmark), calibrated according to ISO 389 (International Organization for Standardization, 1985), according to the ISO 8253-1 standard (International Organization for Standardization, 1989); the air conduction threshold was measured in dB hearing level. The P95 threshold values for presbycusis (for women) were calculated for each patient individually at each frequency in relation to her age (Robinson and Sutton, 1979; International Organization for Standardization, 1984). Only a hearing loss of greater than the P95 value in relation to presbycusis is considered below. A significant discrepancy between the pure-tone threshold and the maximum speech discrimination score was detected by using criteria derived from the reports by Yoshioka and Thornton (1980) and Tymnik et al. (1982).

Tympanograms and contra- and ipsilateral acoustic middle ear muscle reflexes were elicited and recorded with an Amplaid 720 tympanometer and an x/y recorder (Amplaid, Milan, Italy). Reflex thresholds were determined at maximum compliance for the frequencies 0.5, 1, 2 and 4 kHz. Reflexes (at 0.5, 1 and 2 kHz) were recorded with a stimulus of 10 s duration at a hearing level of about 10 to 15 dB above the reflex threshold.

Brain stem auditory evoked potentials (BAEPs) were obtained with a Medelec Sensor AS10/ER94a system (Medelec, Surrey, England) linked to a PC. Details of the method have been described previously (Verhagen et al., 1992).

#### 3.2. Vestibular system

Eye movements were recorded with direct-current electro-oculography (EOG). Eye movement was calibrated before each test by having the patient look in alternation at two light dots  $10^\circ$  on either side of the primary position. Vestibular tests were conducted with the patient in the dark with the eyes open. It was checked whether there was any spontaneous nystagmus.

Velocity step (VS) tests were performed with a rotatory chair (Toennies, Freiburg im Breisgau, Germany). After  $0.8^\circ/s^2$  acceleration and a period of  $90^\circ/s$  constant velocity long enough to let the perrotatory nystagmus response subside, the chair was stopped with  $200^\circ/s^2$  deceleration. The following response parameters were used to characterize the vestibulo-ocular reflex (VOR): initial velocity (V, 90% confidence limits 30 to  $65^\circ/s$ ), time constant (T, 11 to 26 s) and 'Gesamtamplitude' or cumulative eye displacement ( $G = VT$ , 485 to  $1135^\circ$ ) (Huygen et al., 1992; Verhagen et al., 1992).

In the caloric test, the response parameter was the maximum slow phase velocity (SPV) of nystagmus at the culmination of the response, which was obtained by visually selecting some representative and undisturbed beats from the EOG and calculating the average tangent slope.

For the side effect, it was arbitrarily assumed that a relative side difference —  $(\text{difference}/\text{sum})100\%$  — in excess of 20% indicated unilateral hypofunction. The 95% confidence limits of the absolute response level after 20 s irrigation with (150 cm<sup>3</sup>) water at 30°C were 7°/s and 45°/s (Nijhuis and Huygen, 1980). The caloric test was only performed on 2 patients in whom the VS test indicated response asymmetry (Huygen and Nicolassen, 1985).

### 3.3. Ocular motor system

Gaze positions were tested to see whether there was any gaze-evoked nystagmus (in the light, the patient fixating a target at about 30° to 40° lateral displacement). Saccades (20°), smooth pursuit (SP, maximum stimulus velocity 20°/s) and horizontal optokinetic nystagmus (OKN, stimulus velocities 40 and 60°/s) responses were elicited and analysed as reported previously (Verhagen et al., 1992). Vertical OKN was evaluated in cases 4 and 5.

## 4. Results

Case 6 (possible carrier) had completely normal results on all the tests. She is probably unaffected. All the other cases (all definite or probable carriers) showed abnormalities in various combinations.

### 4.1. Auditory system

All 3 definite carriers and the 2 probable carriers (cases 1–5) showed moderate-to-severe sensorineural hearing loss (SNHL). The threshold at 0.5 kHz was in the range of 40–80 dB bilaterally, except for the right ear of case 4 (100 dB). In the high frequency range (4–8 kHz), the threshold was in the range of 100–115 dB, except for the right ear of case 1 (85 dB) and both ears of case 2, who had the best hearing ability (threshold 45–60 dB at 0.5–8 kHz bilaterally). It was remarkable that case 3, who showed thresholds of 40–100 dB at 0.5–8 kHz, had never expressed any complaints about hearing loss. Presumably, this was because she had relatively good threshold levels at the speech frequencies (about 45 dB PTA, i.e., pure tone average at 0.5, 1 and 2 kHz).

Case 3 showed a maximum speech discrimination score of only some 70% bilaterally (not significant), despite her limited hearing loss at the lower frequencies. Case 1 had 0% (i.e., significantly poor) speech discrimination in her left ear, whereas her PTA on the left (80 dB) was only slightly greater than on the right (PTA 70 dB, maximum score 85%). The other cases (2, 4 and 5) showed speech discrimination scores which were in accordance with their PTA values.

Previous audiograms and discrimination scores were available for cases 2, 4 and 5. Case 2 had audiograms and scores at the age of 33 years which were very similar to those obtained at 42 years of age; thus, there had been no progression over the last 10 years. Case 4 had displayed much better hearing thresholds at the age of 6 years than at 21 years of age. The progression in her hearing loss had been about 20 dB at the low frequencies and about 50 dB at the high frequencies, i.e., she showed an average annual threshold increase of about 1 to 3 dB from the low to the high frequencies. Hearing had been steady from 21 to 23 years of age. Case 5 had also undergone hearing examinations at 21 and 23 years of age: according to the speech discrimination scores, her hearing may have been slightly better in the right ear at 21 years of age.

Tympanograms, stapedial reflexes and BAEPs, as far as evaluable, were normal; irreproducible results were obtained from case 1, left, and cases 4 and 5 bilaterally, who had the most pronounced hearing loss.

### 4.2. Vestibular system

Cases 1 and 2 showed vestibular hyperactivity (VH) with a high gain (0.75–0.85, normal limit 0.72, see Methods). Case 2 also showed directional preponderance to the left. Case 4 showed left-beating spontaneous (and gaze-evoked) nystagmus of varying intensity in full light and in the dark, with an average SPV of about 4°/s. Her responses to sinusoidal rotation in the dark (at 0.05 Hz and 50°/s peak velocity) showed clear bias towards nystagmus to the left. This patient also had defective visual suppression of vestibularly evoked nystagmus (see below). Cases 4 and 5 showed marginally high response levels of the VOR, indicating mild VH. Caloric tests were performed only on the cases (2 and 4) who showed asymmetrical responses; the results were normal.

### 4.3. Ocular motor system

Case 2 showed saccadic intrusions: square wave jerks and double saccadic pulses. Cases 4 and 5 showed multiple step hypometric saccades (MSHS), especially to the left, and case 5 also showed hypometria of saccades to the left. Cases 4 and 5 showed marginally low peak velocities of horizontal saccades and this also applied to case 1 for abduction saccades. Cases 1, 4 and 5 showed defective SP and disturbed OKN responses. Case 4 (with nystagmus bias to the left) showed only a modulated OKN to the left; right-beating OKN could not be elicited. Cases 1 and 5 showed significantly low OKN response velocities at 60°/s stimulation (about 32°/s at most in case 5, P95 normal limit at 23 years of age 45°/s; about 35–38°/s for case 1, normal limit at 32 years of age 43°/s). Cases 4 and 5, the only patients in whom this was tested (during sinusoidal rotation), also showed failure of fixation suppression (SPV during fixation > 50% SPV in the dark). Vertical OKN was qualitatively normal in case 5, but in case 4 only downbeating OKN could be elicited.

## 5. Discussion

The neurological signs of the patients with this syndrome consisted of hypotonia, ataxia, muscle weakness, diminished muscle tendon reflexes, nystagmus, visual disturbances and SNHL (Arts et al., 1993). We obtained a report (by Dr. A.G.M. van Vliet, University Hospital Rotterdam) on an oculo-vestibular examination performed with EOG on the only surviving patient (V.5, born in 1979) at the age of 2.5 years. His findings included primary position upbeating nystagmus, gaze-evoked nystagmus, saccadic smooth pursuit and impaired OKN responses (velocity 7–17°/s at 60°/s stimulation); a later report mentions bilateral abducens palsy as an additional finding in this patient at the age of 12 years (Arts et al., 1993).

The carrier females showed a number of noteworthy features. Their SNHL seemed to be of a peripheral (cochlear) nature, given the normal middle ear muscle reflexes and BAEPs, but in case 1 the significant discrepancy between the pure-tone hearing threshold and the maximum speech discrimination score indicated a neural or central abnormality on the left (BAEPs were not available on that side).

VH (high VOR gain) was seen in 2 definite carriers (cases 1 and 2), both of whom had the symptom of dizziness. In the third definite carrier, the VOR gain might have been decreased by the use of sodium valproate, a GABA-ergic drug (Huygen et al., 1994). The 2 probable carriers (cases 4 and 5), who showed a tendency towards VH, also had ocular motor disturbances, which might have reduced their VOR levels by shortening the VOR time constant (Huygen et al., 1990).

Cases 1, 2, 4 and 5 all showed one or more of the following ocular motor abnormalities: saccadic intrusions (case 2), MSHS (cases 4 and 5), (marginally) low saccade peak velocity (cases 1, 4 and 5) and disturbed SP and OKN responses (cases 1, 4 and 5). All of these abnormalities (except for the possible slowing of saccades), as well as the VH (Thurston et al., 1987; Verhagen et al., 1992; Huygen et al., 1994), can be localized to the (vestibulo)cerebellum (including the vermis cerebelli) (Doslak et al., 1983; Sharpe and Fletcher, 1984; Leigh and Zee, 1991). MRI of case 1 revealed mild cerebellar atrophy. SP/OKN impairment, in general, may also be caused by dysfunction of the deep parietotemporo-occipital cortex (Leigh and Zee, 1991).

There was clear cerebral dysfunction in 2 out of the 3 definite carriers and in the 2 probable carriers; 3 of them also had pyramidal tract signs, i.e., exaggerated reflexes and extensor plantar responses. No impairment of posterior column function was found. The signs and symptoms seemed to arise in the carriers in the first and second decades of life. The disorder was severe in the affected males, but it was also prominent and symptomatic in the definite and probable carriers.

The present syndrome shows X-linked inheritance. Linkage studies have located the disease to the long arm of the X-chromosome between Xq22.1 and Xq24, with a maximum lod score of 5.37 (unpublished observation). The carrier females may exhibit signs and symptoms due to partial deficiency of the gene product or due to complete deficiency in some cells through lyonization. To our knowledge, this or a similar disorder has not been described in other families. The present disorder can be distinguished from Friedreich ataxia (FA) by the age of onset and the presence of pyramidal tract dysfunction, while vestibular tests showed hyporeflexia in FA; SNHL is atypical in FA, but abnormal stapedial reflexes have been reported in the early stages of the disease (for review see Verhagen and Huygen, 1994). Obviously, an important difference is that FA is autosomal recessive. This also applies to the syndrome reported by Kallio and Jauhiainen (1985): ophthalmoplegia, hypotonia, ataxia, hypoacusis, athetosis (OHAHA) with an onset at 1–2 years. Ataxia and hypotonia were the first signs, followed by rapidly progressive SNHL; the patients did not show caloric responses. External ophthalmoplegia and athetosis were not seen in the present disorder. In a recent study, Koskinen et al. (1994) presented the OHAHA syndrome as autosomal recessive, infantile onset spinocerebellar ataxia with progressive sensory neuropathy; CT and MRI revealed mild-to-severe cerebellar atrophy in most patients. There was a lack of manifestation in the parents.

Progressive bulbo-pontine paralysis with SNHL shows a more chronic course with severe anterior horn cell degeneration and cranial motor nerve and nuclei impairment; it is probably autosomal recessive. Most patients showed caloric weakness or areflexia (for review, see Verhagen and Huygen, 1994). Abarbanel et al. (1991) suggested X-linked dominant inheritance. Upper motor neuron signs were present in about 20% of their cases but sensory loss was absent. In the literature, most of the affected subjects were female, but Gallai et al. (1981) described an affected girl who had a much more severely affected brother who died at the age of 2 years, which might suggest X-linked recessive inheritance. In all the reports, the parents of affected persons were asymptomatic.

X-linked ataxias are rare. Malamud and Cohen (1958) described early-onset X-linked cerebellar ataxia with optic atrophy, pyramidal tract and extrapyramidal signs and progressive mental deterioration; hearing was not mentioned and the carriers seemed to have no signs or symptoms.

The X-linked cerebellar ataxia described by Shokeir (1970) showed some resemblance to the present disorder, but there was an adolescent onset, normal hearing and no posterior column abnormalities as was reported for the present disorder in affected subjects (Arts et al., 1993); the carriers showed no abnormalities.

Infantile X-linked ataxia with deafness described by

Schmidley et al. (1987) had features comparable with the present disorder, but the neuropathological findings were different from those previously reported (Arts et al., 1993) and the carriers did not seem to have any permanent clinical abnormalities, although the mother of the proband had episodes of ataxia and atrophy of the cerebellum.

Apak et al. (1989) described a family with infantile X-linked ataxia with slower progression, a milder course, normal hearing and other disturbed sensory functions. One definite carrier was normal and one showed hyperreflexia and inconsistent extensor plantar reflexes.

Lutz et al. (1989) reported on infantile X-linked ataxia with similar features, but even slower progression; the carriers had no signs or symptoms; this was also the case in the study by Spira et al. (1979) on a family with X-linked spinocerebellar degeneration with a childhood-adolescent onset.

The disorder described by Farlow et al. (1987) showed an onset in early childhood. Ataxia, although progressive, was much milder and hearing was normal, but there was an adult-onset of progressive dementia. The carriers were asymptomatic. Early-onset X-linked recessive ataxia as reported by Tranebjærg et al. (1992) included (early onset) mental deficiency but apparently no hearing loss. This disorder, however, was not progressive and some of the carriers showed mild symptoms.

Because of bizarre lyonization, almost any X-linked recessive disorder may show manifestation in some heterozygote females (Fried et al., 1969; Bird and Lagunoff, 1978; Cremers and Huygen, 1983; Huygen et al., 1992; Towbin et al., 1993; Van Geel et al., 1994; Pegoraro et al., 1995). Generally, the disorder is much less severe in affected female carriers than in affected males, similar to the situation in the present study.

The present disorder is located in the same area of the X-chromosome as Pelizæus-Merzbacher disease (Gencic et al., 1989) and the complicated form of X-linked spastic paraplegia (SPG2) (Saugier-Weber et al., 1994). Both diseases are caused by mutations of the gene coding for the proteolipoprotein (PLP), which is located at Xq22. However, so far analyses have not revealed deletion or mutation of the PLP gene in the present disorder.

Despite this uncertainty, comparison of these three disorders is interesting. Signs and symptoms common to all three include mental retardation, hypotonia, ataxia, (gaze-evoked) nystagmus, pyramidal signs, optic atrophy and abnormal BAEPs and SSEPs. Similar oculo-vestibular findings in the present disorder and PMD are impairment of SP/OKN responses and slow saccades in the affected males, and VH in the female carriers (Huygen et al., 1992). The PMD carriers did not exhibit any other oculo-vestibular signs, while the present carriers did, as described above. The present disorder is also distinct because of the hearing deficits, peripheral nerve involvement, recurrent infections and the typical fatal outcome (Arts et al., 1993).

Several other syndromes with sensorineural hearing loss have been mapped to the relevant region on the X chromosome (McKusick and Amberger, 1993). At Xq22, apart from the PLP locus, there is also the  $\alpha$ -galactosidase A (GLA) locus which is involved in Anderson-Fabry disease (Bernstein et al., 1989; Morgan et al., 1990) and the type IV collagen  $\alpha$ -5 polypeptide chain (COL4A5) locus which is involved in classical Alport syndrome (Flinter et al., 1989). The gene coding for one of the two subunits (PRPS1) of phosphoribosyl pyrophosphatase synthetase has been localized to Xq22-q24 (Taira et al., 1989); superactivity of this enzyme is found in the syndrome of hyperuricaemia, deafness and neurodevelopmental abnormalities (Simmonds et al., 1982). The findings reported by Rosenberg et al. (1970) in affected persons suggest that they also showed hyperactivity of the vestibular responses (Verhagen and Huygen, 1994).

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