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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 clubfoot, 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 disproportionally 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
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, dysdiado-
chokinesia, ataxic paraplegia, clubfeet, muscle tendon hy-
perreflexia and extensor plantar reflexes. She complained
d 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 gener-
alized 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 ten-
don reflexes and extensor plantar responses. Eye move-
ments 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, dimin-
ished muscle tendon reflexes, dysdiadochokinesia, a pos-
tive 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 otologi-
cal 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), ac-
cording to the ISO 8253-1 standard (International Organiza-
tion for Standardization, 1989); the air conduction
threshold was measured in dB hearing level. The P95
threshold values for presbyacusis (for women) were calcu-
lated for each patient individually at each frequency in
relation to her age (Robinson and Sutton, 1979; Interna-
tional Organization for Standardization, 1984). Only a
hearing loss of greater than the P95 value in relation to
presbyacusis is considered below. A significant discrep-
ancy 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 mid-
dle 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 maxi-
mum 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.,

3.2. Vestibular system

Eye movements were recorded with direct-current elec-
tro-oculography (EOG). Eye movement was calibrated be-
fore each test by having the patient look in alternation at
two light dots 10° 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°/s² acceleration and a period of 90°/s constant veloc-
ity long enough to let the perrotatory nystagmus response
subside, the chair was stopped with 200°/s² deceleration.
The following response parameters were used to character-
ize the vestibuulo-ocular reflex (VOR): initial velocity (V,
90% confidence limits 30 to 65°/s), time constant (T, 11
to 26 s) and 'Gesamtamplitude' or cumulative eye dis-
placement (G = VT, 485 to 1135°) (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 visu-
ally 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 — (difference/sum)100% — in excess of 20% indicated unilateral hypofunction. The 95% confidence limits of the absolute response level after 20 s irrigation with (150 cm³) 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 Nicolasen, 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.

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 features. Their SNHL seemed to be of a peripheral finding in this patient at the age of 12 years (Arts et al. 1988). 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 features. Their SNHL seemed to be of a peripheral finding in this patient at the age of 12 years (Arts et al., 1993).

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 Tranebjaerg 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 Pelizaeus-Merzbacher disease (Gencie et al., 1989) and the complicated form of X-linked spastic paraplegia (SPG2) (Saugier-Veber 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 Galactosidase A (GLA) locus which is involved in Anderson-Fabry disease (Bernstein et al., 1989; Morgan et al., 1990) and the type IV collagen α-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 (Taïra 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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References


