X linked mental retardation and infantile spasms in a family: new clinical data and linkage to Xp11.4-Xp22.11

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Abstract
In order to describe the neurological abnormalities and to identify the gene localisation, we re-evaluated a previously reported family with X linked mental retardation (XLMR). Reliable data were obtained for six of the seven affected males, of whom two had had infantile spasms. Profound MR (IQ<20) was found in one and mild MR (IQ 50-70) in five males. No dysmorphic features, except for macrocephaly in one male, were found. Neurological abnormalities included varying degrees of spinocerebellar involvement. Neuroimaging studies showed abnormalities, such as cerebellar atrophy or corpus callosum hypoplasia or both, in three of the six males. Several affected and unaffected subjects suffered from hyperhidrosis, which appeared to segregate independently as an autosomal dominant trait. Genetic linkage analysis localised the XLMR disease gene to Xp11.4-Xp22.11 with a maximum multipoint lod score of 3.57, overlapping the candidate region reportedly found in two Belgian XLMR-infantile spasm families. Compared to the Belgian patients, the majority of the affected males in this report had a considerably milder phenotype.

Keywords: infantile spasms; mental retardation; spinocerebellar ataxia; X linked recessive syndrome

The number of X linked mental retardation (XLMR) syndromes reported is increasing and, of the 120 current XLMR disorders, 53 have been genetically mapped and 22 cloned.1 In this study, we describe the clinical features and present the results of genetic linkage analysis in a previously reported family with XLMR, which in the absence of recognised metabolic and physical abnormalities had been labelled non-specific XLMR.2 However, clinical data on neurological functioning and neuroimaging in these patients were incomplete and warranted further investigations. Interestingly, two affected males had had infantile spasms (IS), a seizure disorder first reported to be associated with X linked inheritance in a family in 1977.3 The triad of IS, a markedly disturbed EEG pattern called hypersynchrony, and mental retardation (MR) is known as West syndrome. As two Belgian families with non-specific XLMR and West syndrome were recently mapped to Xp11.4-Xpter,4 we wanted to compare the clinical features and linkage analyses in all three families. Also, since several affected and unaffected subjects in the present family had complained of hyperhidrosis, we wanted to determine if this trait also segregated as an X linked condition.

Materials and methods
DATA COLLECTION
The study was performed after obtaining informed consent. Data were collected from a family with seven affected males (patients) through three generations (fig 1). Hospital charts were available for patients III.5, IV.5, and IV.7 (proband). Patient IV.2 had always lived at home with his parents who were alive and could provide reliable clinical data. Information about neurodevelopment in infancy and childhood, particularly with regard to seizures, was unreliable in patients II.2, II.10, and III.5, as their charts from special schools and institutions could not be obtained.

CLINICAL INVESTIGATIONS
The clinical investigation of the six living patients consisted of a neurological, funduscopic, and physical examination. Measurements of the occipitofrontal head circumference and height allowed estimation of head circumference centiles.1 Unsteadiness of gait was graded as mild, moderate, or severe, tendon reflexes as normal or hyperactive, and plantar responses as normal or inverted. Spinocerebellar dysfunction was considered to be present when gait unsteadiness was combined with either plantar inversion or hyperreflexia or both.

The neuropsychological investigation included screening of general cognitive functioning with the Mini Mental State Examination, intelligence quotient (IQ) testing with the Wechsler Adult Intelligence Scale-Revised (WAIS-R, five subtests), language functioning with the Token Test (36 items) and the Boston Naming Test (first 20 items), non-verbal problem solving with Raven Colored Progressive Matrices, memory functioning with Wechsler Memory Scale-Revised Visual Reproduction I, and motor functioning with Finger Tapping and Grooved Pegboard (dominant hand) tests.

The scores of these tests were given as raw scores in order to show the variations between the subjects. Neurodevelopment in patient IV.7 was only evaluated with Griffith’s Develop-
mental Scale owing to very low cognitive functioning. Supplementary laboratory investigations included neuroimaging with cerebral MRI or CT and standard EEG. Chromosome analysis, DNA analysis for fragile X syndrome, and serum values for copper, ceruloplasmin, creatine kinase, uric acid, triglycerides, total cholesterol, free thyroxine, and thyroid stimulating hormone were normal in all patients. Urine gas chromatography-mass spectrometry and automatic amino acid analysis for detection of organic and amino acids was performed in patient IV.7 with normal results.

To determine the mode of inheritance of the hyperhidrosis we studied a sample of 13 subjects, including the six XLMR patients, three obligate female carriers, three healthy males, and one healthy female (fig 1). Assessment of hyperhidrosis depended on the history of excessive sweating, combined with measurement of skin hydration by means of electrical admittance recordings (Sensoderm) in 10 different places. The subjects were recumbent in a room with a temperature of 22-24°C, while physical and psychological stresses were reduced to a minimum. Differences between the test subjects and 13 normal sex and age matched persons were considered significant when p values were <0.05 using the Mann-Whitney test.

**DNA ANALYSIS**

Genomic DNA was extracted from venous blood according to standard procedures. Thirty-three highly polymorphic microsatellite markers spread over the X chromosome were analysed. Polymerase chain reaction (PCR) amplifications of these markers were performed using fluorescein labelled locus specific primer pairs (Genome Data Base). Marker genotypes of patients and relatives were determined by separation of PCR products on a Pharmacia ALF automated sequencer (Pharmacia Biotech, Uppsala, Sweden). Optimised PCR conditions, gel loading, and running conditions can be obtained from the authors.

**GENETIC LINKAGE ANALYSIS**

Two point and multipoint lod score analyses were performed using the Linkage Package 5.1 and FASTLINK version 2.2. Map locations, genetic distances, and allele frequencies were obtained from the Genome Database and from the Généthon data. For males, penetrances were set at 0.0 and 1.0 for non-carriers and carriers of the disease gene, respectively. For females, penetrances were set at 0.0 for non-carriers and heterozygous carriers and at 1.0 for homozygous carriers of the disease gene.

**Table 1** Neurological abnormalities in seven patients in a family with XLMR

<table>
<thead>
<tr>
<th>Patient (age in years)</th>
<th>Seizures</th>
<th>IQ</th>
<th>Neuroimaging</th>
<th>Hyperactive reflexes</th>
<th>Plantar inversion</th>
<th>Unsteady gait</th>
<th>Congenital spinocerebellar dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV.7 (14)</td>
<td>Yes*</td>
<td>&lt; 20</td>
<td>CT normal</td>
<td>Yes</td>
<td>Yes</td>
<td>+++</td>
<td>Yes</td>
</tr>
<tr>
<td>IV.5 (24)</td>
<td>Yes*</td>
<td>61</td>
<td>MRI normal</td>
<td>Yes</td>
<td>Yes</td>
<td>+</td>
<td>Yes</td>
</tr>
<tr>
<td>IV.2 (31)</td>
<td>NR</td>
<td>63</td>
<td>MRI normal</td>
<td>Yes</td>
<td>No</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>III.5 (43)</td>
<td>Yes†</td>
<td>60</td>
<td>MRI cerebellar atrophy, corpus callosum hypoplasia</td>
<td>No</td>
<td>No</td>
<td>+</td>
<td>Possible</td>
</tr>
<tr>
<td>III.8 (50)</td>
<td>NR</td>
<td>57</td>
<td>MRI cerebellar atrophy</td>
<td>Yes</td>
<td>No</td>
<td>+</td>
<td>Possible</td>
</tr>
<tr>
<td>II.10 (68)</td>
<td>NR</td>
<td>60</td>
<td>MRI corpus callosum hypoplasia, cerebral and cerebellar lesions‡</td>
<td>Yes</td>
<td>No</td>
<td>+</td>
<td>Possible</td>
</tr>
<tr>
<td>II.2 (Died aged 30)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Infantile spasms, †tonic clonic seizures, ‡lesions of unknown aetiology, §prolonged residence in an institution for the mentally retarded. CT=computed tomography, MRI=magnetic resonance imaging, MR=mental retardation, NR=not reported, XLMR=X linked mental retardation, - not present, + mild, ++ moderate, +++ severe.

Figure 1. The pedigree structure shows X linked inheritance of mental retardation. DNA was available from subjects labelled DNA. Subjects with a positive test for hyperhidrosis are labelled H+ and the one with a negative test (III.5) is labelled H-.

Figure 2. Patient IV.7 showing macrocephaly, increased flexor tone in the upper extremities, and spastic-ataxic posture of the lower extremities.
**Table 2**  Clinical data and linkage analyses in the three genetically mapped XLMR families

<table>
<thead>
<tr>
<th>Items</th>
<th>Class et al* (2 families, 8 patients)</th>
<th>This report (1 family, 7 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental retardation</td>
<td>8/8</td>
<td>7/7</td>
</tr>
<tr>
<td>Profound mental retardation</td>
<td>8/8</td>
<td>1/7</td>
</tr>
<tr>
<td>Infantile spasms</td>
<td>8/8</td>
<td>0/7</td>
</tr>
<tr>
<td>Early death (&lt;20 years)</td>
<td>5/8</td>
<td>3/6</td>
</tr>
<tr>
<td>Head circumference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;75th centile</td>
<td>1/1*</td>
<td>3/6</td>
</tr>
<tr>
<td>&gt;97th centile</td>
<td>0/1</td>
<td>1/6</td>
</tr>
<tr>
<td>Spino cerebellar ataxia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0/8</td>
<td>2/6</td>
<td></td>
</tr>
<tr>
<td>Cerebellar atrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/4†</td>
<td>2/6</td>
<td></td>
</tr>
</tbody>
</table>

* Measurement reported in only one patient.
† Appropriate investigations were reported in four patients. Cortical cerebral and cerebellar atrophy was shown in one of the two patients in whom brain necropsy was performed, while cerebellar MRI was normal in two others.

**Results**

**CLINICAL DATA**

Details of the clinical characteristics are shown in table 1. Seizure abnormalities included IS and hypsarrhythmic EEG patterns with onset at 4 to 6 months of age in patients IV.7 and IV.5, which responded promptly to corticosteroid treatment. However, neurodevelopment in the younger brother (fig 2) was profoundly delayed as he never developed expressive vocal language and had a very ataxic gait. Patient III.3 had idiopathic epilepsy with generalised tonic-clonic seizures from the age of 11 years. He was initially treated with phenytoin and later lamotrigine was added. The interictal EEG showed 4-6 per second slow rhythm with frequent epileptiform discharges. The retinae appeared normal on fundoscopy in all patients.

Spino cerebellar dysfunction was considered to be present in patients IV.7 and IV.5 and possible in III.5, III.8, and II.10 (table 1). Patient IV.7 (fig 2), who had not learned to walk independently before 9 years of age, had moderate limb stiffness and marked gait ataxia, suggesting pyramidal tract and cerebellar involvement. Patient II.10 had marked gait ataxia as, for example, he could not stand on one foot. A history of delayed independent walking until 5 years of age indicated congenital spinocerebellar dysfunction. Surprisingly, cerebral MRI showed lesions in both cerebellar and cerebral hemispheres resembling ischaemic infarcts. However, no risk factors for cerebrovascular disease were detected and a Doppler ultrasound examination of the precerebral arteries was normal. Episodes suggestive of acute stroke during the last 20 years were not reported.

No dysmorphic findings were present in any of the patients, but the head circumference was 1 cm >97th centile in patient IV.7, and ranged between the 75th and 97th centile in patients III.5 and III.8, and between the 10th and 75th centile in the others.

Estimated IQ scores on WAIS-R were 57-63 in five patients, corresponding to mild MR, and <20 in patient IV.7, corresponding to profound MR. IQ estimation of patient II.2 was not possible. He had lived in an institution for the mentally retarded from the age of 11 years and died aged approximately 30 years. The mean value and range of scores (shown in parentheses) on the neuropsychological tests for the five patients with mild MR were: Mini Mental State examination (max 30): 14 (0-18), Raven Colored Progressive Matrices (max 36): 10 (0-12), Token Test (max 36): 12 (1-16), Boston Naming Test (max 60): 11 (6-12), Visual Reproduction (max 41): 0 (0-15), Finger Tapping (normal 50): 28 (11-42), and Grooved Pegboard (normal 60): 300 (250-300). The patients exhibited a shy and friendly personality, although postictal violent behaviour occurred regularly after seizures in patient III.5. The female obligate carriers in the pedigree had never had seizures and all were of normal intelligence.

Twelve of the 13 subjects examined in the study sample had a history of excessive sweating, 10 in the palmar/plantar region. Skin moisture was significantly increased in this region compared to controls, while measurements from the forearm, forehead, and axillae did not significantly differ from the controls. As shown in the pedigree (fig 1), hyperhidrosis was not inherited as an X linked trait.

**GENETIC LINKAGE STUDY**

The results from the two point linkage analysis are shown in table 3. The maximum lod score (Z=3.291) was obtained with marker DXS8090 at theta 0.0. All the markers located between DXX7593 and DXS8012 were linked to the disease gene and yielded positive lod scores at theta 0.0, but none of them was fully informative. Markers DXS8051, DXS8099, and DXS1003 also yielded positive lod scores at theta 0.0, but this was because of incomplete informativeness. The results of the multipoint linkage analysis are shown in fig 3. The linked region extended from DXX7593 to DXS8012 with a maximum lod score of 3.7. A region with
Lod score was 3.57. Distally to DXS8012 proximally, in the cytogenetic area Xp11.4-Xp22.11. The maximum lod score curve was

**Figure 3** Multipoint linkage analysis. The candidate region extended from DXS7593 distally to DXS8012 proximally, in the cytogenetic area Xp11.4-Xp22.11. The maximum lod score was 3.57.

A positive lod score (0.9) appeared on Xq28, between markers DXS8043 and DXS1193. However, all markers tested in this region showed at least one recombinant. The overall probability that the gene was located in this region was 1/625 compared to the region between DXS7593 and DXS8012. From these data, we could conclude that the candidate region extended from DXS7593 to DXS8012, corresponding to the cytogenetic localisation Xp11.4-Xp22.11, a large region of about 25 cM.

**Discussion**

The clinical features in the present family included varying degrees of impairment in all motor and cognitive domains. There was also marked heterogeneity regarding spinocerebellar involvement and seizures. Interestingly, neurodevelopment in the two brothers with IS deviated markedly, although the seizures and hypersrrhythmia resolved promptly on corticosteroid treatment. Congenital non-progressive spinocerebellar ataxia was found in two patients and was also suspected in three others, including patient II.10 who had a history of gross motor delay in childhood. In patient III.5, no corticospinal involvement could be found, but cerebral MRI showed marked atrophy of the cerebellar vermis (table 1). This could be the result of prolonged treatment with phenytoin, although serum levels had always been adequately controlled. However, coexistence of mild hypoplasia of the corpus callosum in this patient may indicate that cerebellar atrophy was genetically determined rather than drug induced. Distinct craniofacial abnormalities were not observed, although patient IV.7 was macrocephalic.

Marked phenotypic variation has been observed with other X linked genetic mutations causing XLMR and neurological symptoms, for example, mutations in the gene for the L1CAM cell adhesion molecule. 11 12 13 XLMR associated with widespread neurological abnormalities, including corticospinal tract degeneration, has been reported in two distinct syndromes 12 13 mapped to the long arm of the X chromosome. X linked ataxia-deafness-optic atrophy syndrome 14 could be excluded on clinical grounds. IS resulting from Aicardi syndrome (MIM 304050) could also be excluded, as this is a non-familial condition restricted to females because of X linked dominant mutation.

Linkage analysis showed that the responsible gene in the present pedigree was located in Xp11.4-Xp22.11. In a previous report on two Belgian families, the gene was mapped to Xp11.4-Xpter. Therefore, the linkage data were compatible with the hypothesis that in all three families the same genetic factor was responsible. This gene would then be located between DXS7593 (the distal flanking marker in the family described here) and DXS1068 (the proximal flanking marker in the two other mapped families), leaving a candidate region of approximately 17 cM. With the exception of our patient IV.7, the Belgian families were more severely affected (table 2). In both cases the candidate chromosome region is very large, and although they overlap, it is possible that different genes are involved. The prompt response to corticosteroid treatment for IS in our family may indicate a different primary brain pathology. Spinocerebellar ataxia was not reported in the Belgian patients, although this clinical feature may have been overlooked owing to severe psychomotor retardation. Interestingly, cortical cerebral and cerebellar atrophy was reported in one of the two patients in whom brain necropsy was performed, while cerebral MRI was normal in two other patients.

Alternatively, this family might represent a new syndromic entity, or belong to a heterogeneous group of conditions designated non-specific X linked MR. 15 As syndromic XLMR is confined to diseases with consistent and specific biochemical, neurological, or dysmorphic abnormalities, 16 the condition described in this report could be labelled non-specific XLMR until the disease gene is identified. A series of other non-specific XLMR conditions have also been localised to the short arm of the X chromosome, 17 but not with clinical features similar to our patients.

Detailed clinical and laboratory investigations of a representative sample of people in the pedigree (fig 1) showed that increased sweating segregated as an autosomal dominant condition, suggestive of the hyperhidrosis palmaris et plantaris syndrome (MIM 144110).

In conclusion, we investigated a family with XLMR in which linkage analysis located the disease gene to Xp11.4-Xp22.11. Although the clinical findings were variable, seizures and non-progressive spinocerebellar ataxia occurred in several of the patients and distinguished them from other reported entities with XLMR.
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