Autosomal recessive oculopharyngeal muscular dystrophy

Summary. Oculopharyngeal muscular dystrophy is known as a rare autosomal dominant disease. A family is reported suggesting that there may be genetic heterogeneity in oculopharyngeal muscular dystrophy and that in some families the mode of inheritance may be autosomal recessive.

Progressive dystrophy of external ocular muscles (ocular myopathy) was reviewed by Kiloh and Nevin (1951). In 1962, Victor et al described and gave the name of oculopharyngeal muscular dystrophy to a familial disease of late life characterized by dysphagia and progressive ptosis of the eyelids. Their report included a sporadic case and a family which demonstrated an autosomal dominant mode of inheritance. Since then several families and some single case reports have been published and the nosological entity of oculopharyngeal muscular dystrophy has been accepted as a hereditary disease due to an autosomal dominant gene (Hayes et al, 1963; Schotland and Rowland, 1964; Teasdall et al, 1964; Bray et al, 1965; Aarli, 1969; Graf, 1971; Penchazadeh and Teasdall, 1971; Szobor, 1973).

The purpose of this report is to present a family suggesting that there may be genetic heterogeneity in oculopharyngeal muscular dystrophy and that in some families the mode of inheritance may be autosomal recessive.

Case reports

The proposita, case 1 (VI.10, Fig. 1), was the youngest in her sibship. The family is Ashkenazi Jewish of Hungarian origin. The parents of the proposita are both first cousins once removed and third cousins. An older sister, case 2 (VI.9), is also affected. The rest of the family is reported to be without muscle disease except one distant relative (V.3) who is said to have a disease similar to that of the two sisters. This relative is herself the product of first-cousin marriage. She lives abroad and unfortunately details of her condition were not available. Both parents and the eldest brother of the proposita were personally examined. The father and mother were found to be in good health and without muscle weakness at the age of 75 and 70, respectively. The three brothers were healthy at ages 47, 46, and 40 years.

Case 1. (VI.10) is a 37-year-old woman, mother of three healthy children. From the age of 34 she noticed mild bilateral ptosis, and gradually she developed difficulty in looking forward. There were no other complaints. The patient was admitted to the Neurology Department for investigation. She used to wrinkle her forehead and extend her neck in an attempt to look forward. She never had double vision. Neurological examination revealed bilateral symmetrical ptosis (Fig. 2) down to the midpupillary level. The facies was expressionless. Eye movements were limited in all directions but especially upwards. The patient was not able to raise her eyes above the horizon but there was no limitation in convergence. The rest of the neurological examination revealed bilateral drop foot and the ankle reflexes could not be elicited. There was no myotonia or muscle fibrillation. The gag reflex was reduced on both sides. Chest radiology was normal and the thymus was not enlarged. EEC and ECG were normal. CKP and LDH levels were normal. EMG of the lateral recti of both eyes showed potentials of low amplitude and short duration and no fibrillation was observed, indicating a primary muscle disease. EMG of the orbicularis oculi and of the frontalis muscle
then she noticed stairs. Sometimes she had difficulty swallowing and while drinking she sometimes coughs. She also complained of difficulty in climbing stairs. Examination revealed a thin woman with bilateral ptosis down to the midpupillary level (Fig. 3). The facies was expressionless. Symmetrical limitation in elevation of the eyes up to the horizontal level was observed as well as a limitation of lateral gaze movement.

Depression of the eyes and convergence were found to be normal. A bilateral weakness of the orbicularis oculi was noticed. Speech had a nasal character with a monotonous melody and low volume. The tongue movements were clumsy. A paresis of the right vocal cord was observed.

The gag reflex was reduced on both sides. Standing up from the recumbent position was impossible without support from the arms. Bilateral knee and ankle jerks could not be elicited. The ECG was normal. There was no myotonia or muscle fibrillation. Thyroid function tests were normal.

EMGs of frontalis, orbicularis oculi, and left lateral rectus muscles showed a severe myopathic pattern. The Tensilon test was negative.

**Case 2.** (VI.9) An older sister of the proposita is a 40-year-old woman, the mother of a healthy son.

Since the age of 35 she noticed mild bilateral ptosis. She gave birth to her only son at the age of 39 and since then she noticed that her voice had become weak and she had difficulty in pronouncing lingual letters. She had some difficulty in swallowing and while drinking she sometimes coughs. She also complained of difficulty in climbing stairs. Examination revealed a thin woman showed a severe myopathic pattern. The right gastrocnemius and left deltoid muscles showed normal potentials. Nerve conduction (right common peroneal) was normal (52 m/s). The Tensilon (edrophonium chloride) test for myasthenia gravis was negative.

**Fig. 2.** Case 1 (aged 37 years) showing bilateral ptosis.

**Fig. 3.** Case 2 (aged 40 years) showing bilateral ptosis.

**Discussion**

Oculopharyngeal muscular dystrophy is known as an autosomal dominant affection. The age of onset is usually between 45 and 60 years. The disease generally begins with ptosis of the eyelids followed after a brief interval by dysphagia. Bilateral ptosis of the eyelids and involvement of the pharyngeal musculature is essential for the diagnosis. The clinical picture of the two sisters described in this report is very similar to that of the autosomal dominant form of the disease except that the age of onset, in the mid 30s, is somewhat earlier than the usual age of onset in the dominantly inherited disease. As the 75-year-old father and the 70-year-old mother did not show any sign of the disease, simple dominant mode of inheritance can be ruled out. The consanguinity of the parents and the absence of history of muscle disease among relatives in previous generations, except for one report affected who is herself the result of a first-cousin marriage, lend further support for an autosomal recessive mode of inheritance.

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**References**


Partial trisomy for the long arms of chromosome No. 5 due to insertion and further ‘aneusomie de recombinaison’

Summary. Five members of a family with a balanced insertion (1;5)(q32; q11q22) are presented. The daughter of one of them shows multiple malformations and a partial trisomy for the long arms of chromosome No. 5 (5q11 to 5q22 segment) resulting from a ‘aneusomie de recombinaison’ in her mother. The propositus’ karyotype is 46,XX,rec(1;5)ins(1;5)(q32;q11q22). This case is the first reported example of an insertion between two chromosomes followed by ‘aneusomie de recombinaison’. It also is the first reported case of trisomy involving the long arms of chromosome No. 5.

Exchanges of genetic material between two chromosomes may be due to reciprocal translocations or to insertions. Most of them are of the first type and many studies using the more accurate fluorescence or denaturation techniques have been reported. Such disorders may cause trisomy or partial monosomy in the offspring of the balanced individuals by an incorrect disjunction of the involved chromosomes at meiosis. Insertions seem rarer still and, as they lead to the formation of a loop during meiosis, a crossing-over in this loop may result in a genetic imbalance, the so-called ‘aneusomie de recombinaison’ (Lejeune and Berger, 1965).

Very few cases of ‘aneusomie de recombinaison’ have been published. Some of them have not been investigated by the banding techniques. They are likely to be found, however, where identical chromosome structural anomalies occur in two individuals of the same family, but only one shows clinical symptoms, or where new types of aberration occur in the offspring, apparently due to a balanced rearrangement (insertion or pericentric inversion) in one of the parents, and where such chromosomes are unexplained by the usual mechanisms of chromosome disjunction (Grouchy and Gabilan, 1965; Lejeune and Berger, 1965; Grouchy et al, 1966; Hoehn et al, 1971; Cantu, 1972; Neu and Gardner, 1972). Other cases have been ascertained positively by analysis of the banding patterns (Caspersson et al, 1971; Boué and Boué, 1973; Dutrillaux et al, 1973; Taysi et al, 1973; Therkelsen et al, 1973).

Published cases of insertions are also scarce in the literature. As in the case of ‘aneusomie de recombinaison’ some of them may be inferred (Grouchy and Gabilan, 1965; Lejeune and Berger, 1965; Grouchy et al, 1966; Hoehn et al, 1971; Cantu, 1972; Neu and Gardner, 1972) while others are definitely ascertained by analysis of banding patterns (Grace et al, 1972; Gray et al, 1972; Rethoré et al, 1972; Taillemite et al, 1973; Therkelsen et al, 1973).

Among these insertions, only the case reported by Therkelsen et al (1973) proved to be an ‘aneusomie de recombinaison’—namely, an intrachromosomal insertion involving a chromosome No. 2.

In the paper we report the first case of insertion between two chromosomes followed by ‘aneusomie de recombinaison’.

Case report

The pedigree of the family is shown in Fig. 1. The index case is a girl whose birthweight was 2880 g, and who was born at term after an uneventful pregnancy. The parents are not consanguineous. They are in good health and young; the mother is 24 years old and the father 23 years old. The propositus was examined for the first time at the age of 3 years 7 months. The parents reported slow development of motor functions. The child was not able to sit until 18 months and could not stand until 2 years. Feeding has always been a problem and vomiting is frequent.

Clinical examination (Fig. 2) shows general hypotrophy (11 300 g) but a normal height (95 cm). Spon- taneous activity is scarce and there is an overall muscular hypotrophy associated with severe muscular atrophy; the child is unable to sit when in a lying position and she must be aided to maintain a standing position. Walking is difficult and climbing stairs impossible.

She smiles and seems affectionate but does not talk.

IQ is 64. Osteotendinous reflexes are normal as is the EEG. The cranial circumference is slightly diminished (48 cm).
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doi: 10.1136/jmg.12.4.416

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