
FAMILIAL MYASTHENIA GRAVIS

REPORT OF FOUR CASES

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Myasthenia gravis (MG) is considered a noninherited, sporadic and uncommon disease^{5,12}. The familial occurrence of MG is very rare according to most authors^{2, 3, 4, 5, 6, 13, 14, 17}.

Among 145 patients with MG followed up in the last 20 years in the Neurological Clinic of the University of São Paulo Medical School, two pairs of siblings from two families without parental involvement were studied. Our cases are the first in Brazil, considering the best of our knowledge.

REPORT OF CASES

CASE 1 — A 11-year-old white Brazilian girl had bilateral and symmetric partial ptosis, noted since the first months of age by her parents. Her upper lids drooped more at the end of the day. Difficulty for looking far, frequent falls during the gait and an inconstant and transient double vision were referred. The patient was born after normal pregnancy, labor, and delivery. The fetal movements have been normal. Crying and sucking were normal in the nursery. The developmental history is normal. She had measles and varicella. The parents are in good health and without consanguinity. Her brother is affected with the same disease (case 2). Clinical examination was normal. No mental abnormality was observed. Neurological findings consisted in ptosis of both eyelids, with partial external ophthalmoparesis. The pupils were round, regular, and equal and reacted to light but not in accommodation. Bifacial weakness was present, resulting in an incomplete occlusion of the eyes. The head was held slightly forward. There was widespread muscular weakness, particularly in the proximal limb-girdle. The muscle weakness was rapidly increased by exercise (Fig. 1, left side). Other findings were normal. Laboratory investigations and Roentgen studies of the chest with planigraphy were normal. The electromyographic study of the orbicularis oculi muscles showed the characteristic response of MG (Fig. 2). The edrophonium chloride

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injected intravenously produced objective improvement of the ocular symptomatology. Following the injection the patient felt an intense pain into the eyes. Identical symptom was referred during the treatment with prostigmine by oral route. This treatment produced a marked improvement of the muscle weakness of the limbs but not of the ocular muscle. Immunoelectrophoresis of the serum proteins was normal. Thyroid tests were normal.

CASE 2 — A 7-year-old white Brazilian boy, brother of case 1, had bilateral and symmetric partial ptosis, noted since the first months of age by his parents. Generalized muscle weakness was only noted some time later. The disability was worse towards the evening, when the ptosis was also more prominent. A prolonged conversation produced a fading voice (nasal speech). Sometimes the patient presented a difficulty in chewing and swallowing. Birth and developmental history were normal (case 1). The mother was well during pregnancy. The fetal movements have been normal. Labor was normal and no abnormality occurred at birth. He walked at the age of one year and half. Measles at four years of age followed by hypoacusis. The physical examination showed only a testicular defect (atopic glands). No mental retardation was noted. The neurological examination showed a global muscular hypotonia, a light weakness in the four limbs, specially in its proximal parts, external ophthalmoparesis in both sides, and a bilateral and symmetric weakness of the orbicularis oculi muscles. There was no convergence. Bilateral and symmetric ptosis was seen (Fig. 1, right side). Other findings were normal. Laboratory investigation and Roentgen studies of the chest were normal. The electromyographic study of the orbicularis oculi muscles showed the same myasthenic disorders as observed in case 1. Following the intravenous administration of edrophonium chloride there was prompt and transient relief of symptoms and restoration of ocular movements and disappearance of ptosis; the treatment with prostigmine by oral route promoted an improvement of the muscle weakness but not of the ophthalmoparesis. The immunoelectrophoresis of serum proteins was normal. Thyroid tests were normal.

CASE 3 — A 24-year-old white Brazilian man had bilateral and symmetric partial ptosis, noted since four months of age. Muscle weakness in the four limbs was observed later, specially in the proximal muscles. Paresis of the extraocular muscles and of the orbicularis oculi in both sides was present. The symptomatology was symmetric and was worse towards the evening. Sometimes the patient tried chloride the ptosis disappeared and the ocular motions returned to almost normal a light difficulty in chewing and swallowing. The patient was born after normal pregnancy, labor and delivery. Crying and sucking were normal. The development was apparently normal. His parents were in good health and without consanguinity. His sister is affected by the same disease (case 4). A brother is epileptic and another one is a mental deficient. Clinical and psychiatric examinations were normal. Neurological findings consisted in symmetric partial ptosis of the upper eyelid with bilateral and partial external ophthalmoparesis. There was a generalized muscular weakness, mainly in the proximal parts of the lower limbs and in the orbicularis oculi muscles. Light dysphagia and dysarthria and moderate difficulty in chewing occurred sometimes. The pupils were normal and reacted well to light. Convergence was absent (Fig. 3, left side). Laboratory investigations and Roentgen studies of the chest were normal. The pneumoplanimediastinography showed a suggestive image of hypertrophic thymus in the superior mediastinum (Fig. 5). Thyroid tests were normal; thyroid antibodies were not detected. The electrocardiogram was normal. Histological examination (biopsy of the lateral rectus muscle) showed: interstitial edema and light hystiocytic proliferation; the end-nerve and muscular fibers were normal. The electromyogram of the deltoid and quadriceps femoris muscles in both sides and of the right levator palpebrae superioris showed disorders of myasthenic type. Following intravenous administration of edrophonium



Fig. 1 — Case 1 (left side) and case 2 (right side). Partial ptosis of both eyes and bilateral external ophthalmoparesis.

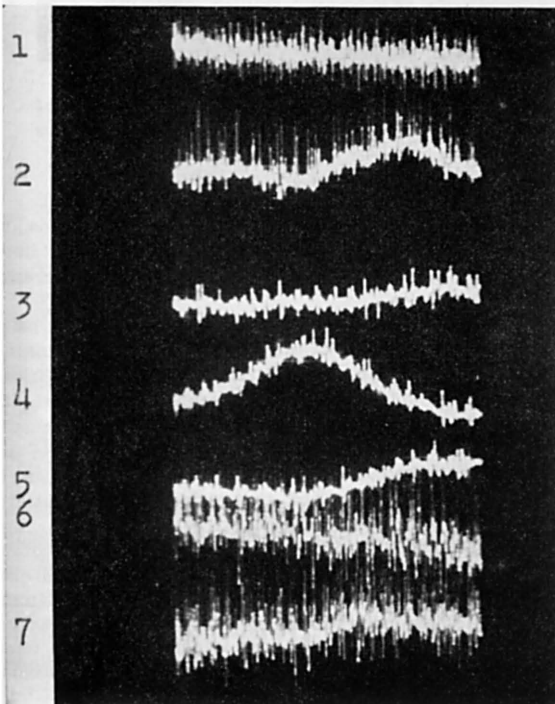


Fig. 2 — Case 1.
Electromyography of the orbicularis oculi muscles.



Fig. 3 — Case 3 (left side) and case 4 (right side). Identical picture as observed in cases 1 and 2 (Fig. 1).



Fig. 4 — Case 3 (left side) and case 4 (right side). Improvement after the administration of edrophonium chloride by venous route in both cases.

activity (Fig. 4, left side)). The immunoelectrophoresis of serum proteins was normal. The treatment with prostigmine by oral route was followed by improvement of the muscular weakness in the limbs but not of the ophthalmoparesis.

CASE 4 — A 14-year-old white Brazilian girl, sister of case 3. Bilateral partial ptosis was noted at approximately four months of age. A moderate weakness in the four limbs appeared later. Sometimes the patient referred a slight difficulty in breathing. Birth nursery conditions and further development were normal. Clinical and psychiatric examinations were normal. The neurological examination showed a marked bilateral external ophthalmoparesis with a partial ptosis in both eyes; symmetric paresis of the orbicularis oculi; light proximal weakness in the four limbs mainly in the lower ones. The pupils and their reactions to light were normal. Laboratory investigations and Roentgen studies of the chest with pneumo-planimediastinography were normal. Thyroid tests were normal. Electromyography of the orbicularis oculi and of the levator palpebrae superioris muscle in both sides showed alterations of myasthenic type. The edrophonium chloride test (1 mg) by venous route was followed by prompt relief of symptoms and partial recovery of ocular movements and an improvement of ptosis (Fig. 4, right side). The immunoelectrophoresis of serum proteins was normal. The treatment with oral prostigmine showed no influence on the ophthalmoparesis.

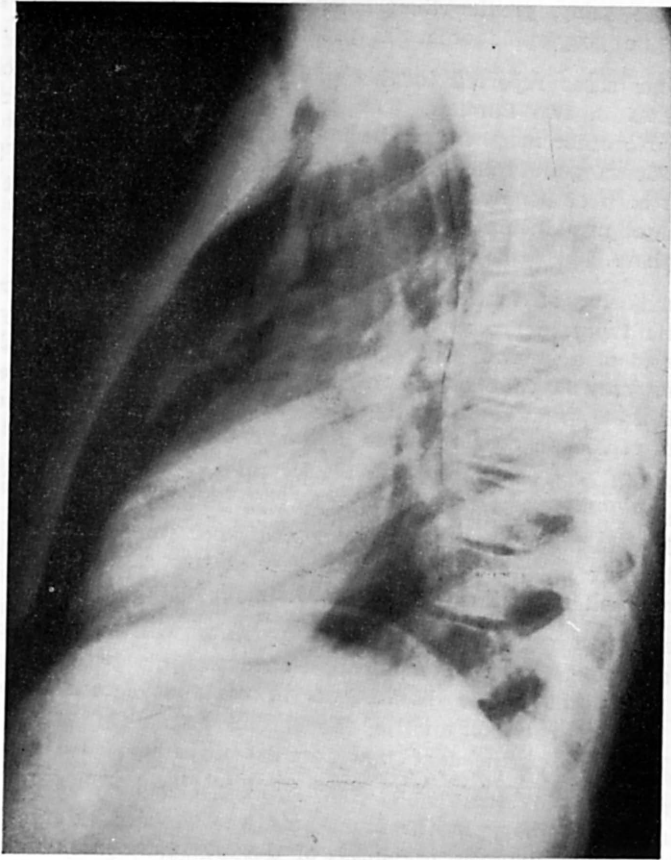


Fig. 5 — Case 3. Pneumomediastinography.

DISCUSSION

Only 4 among 145 patients with MG have presented familial characteristics. One of them (case 3) has been followed up for 12 years. The rarity of familial MG has been emphasized by many authors^{1, 3, 5, 6, 13, 17}. In our group the incidence of familial MG (2.7%) is in agreement with the incidence in other series¹⁰. These findings confirm the low frequency in regard to the incidence of MG in the general population, which is estimated from 1 in 10,000 to 1 in 40,000 persons^{5, 13}. The familial incidence of MG really is rare, with 65 cases reported in 29 families in the medical literature between 1900 and 1964^{1, 6}. Until 1966 about 80 cases were reported in 36 families. In 1971, Namba et al.¹⁰ reported 164 patients in 73 families, estimating the familial occurrence, excluding neonatal myasthenia, in 3.4%,

this incidence being, greater than in the general population ($P < 0.001$). There was no geographic or racial predilection of familial MG¹⁰.

The four cases reported in this paper represent two pairs of sibling of both sexes in two families. The parents are healthy and not consanguineous. No other members of the immediate or near family are similarly affected. Consanguinity is uncommon^{4, 10, 13}; except one case¹⁵ all the other cases were born of nonmyasthenic mother^{13, 15}. This is in contrast to transient neonatal myasthenia which invariably occurs in infants born of myasthenic mothers.

The majority of familial occurrences are in sibships, particularly in monozygotic twins, or cousins of first generation^{10, 13}. It is very rare to detect the disease in two generations of the same family^{12, 17}. Until 1969 there were only 7 families involving two generations^{4, 8}. There are no reports of three generations being affected^{8, 12}, until 1973. There weren't other cases of MG in near relatives in the families of our patients.

The symptomatology was noted during the first few months after birth in our cases. The prominent symptom was a bilateral partial ptosis of the eyelids. In all cases the pregnancy and labor were normal. The fetal movements were apparently normal at least in two cases (cases 1 and 2). All children had normal crying and sucking at birth.

There was a greater proportion of patients with familial myasthenia starting at younger ages, compared with myasthenic patients in general, in whom the onset of the disease was in the first decade in only 3.5% (2% to 7%) of patients and in the second decade in 14.7% (10% to 20%)¹⁰. In spite of the fact that familial myasthenia usually starts at birth or during infancy^{9, 10}, later ages of onset have been reported¹⁰.

The symptomatology in the four cases was similar: external ophthalmoparesis with bilateral ptosis; weakness of the orbicularis oculi muscles; light weakness in the four limbs, specially in its proximal segments; persistence and stabilization; resistance to drugs, except in one patient (case 3) in whom a significant improvement of the limbs was observed with treatment. Mental deficiency was not observed. The incidence of mental retardation amongst familial cases is seven times that of the general population (estimated in 1% or less)⁴. The oculofacial signs were early and prevalent in the four cases. No thymoma was seen. The pneumomediastinography done in two cases (cases 3 and 4) showed in the case 3 a suggestive image of hypertrophic thymus (Fig. 5). Thymoma or hypertrophic thymus associated to familial MG is exceptional^{1, 10, 17}. The lack of careful investigation (pneumomediastinography or thymic venography) and the low number of thymectomies performed may explain this fact.

Thyroid function was normal in the four cases. Hyperthyroidism associated with familial MG, specially in monozygotic twins, has been described¹¹. Immunoelectrophoresis of serum proteins, done in the four patients, was normal.

Electromyogram of the orbicularis oculi muscle showed typical myasthenic features in three cases, and the same response was obtained of the levator palpebrae superioris and extraocular muscles in two cases (cases 3 and 4).

The evolution of the four patients has been favorable, seemingly protracted or stabilized. This fact is frequently observed in familial MG. The mortality rate is low and the prognosis is good. Our four patients are being followed for further investigations.

SUMMARY

Two pairs of siblings with myasthenia gravis, belonging to two different families, are reported. This is the only record of familial myasthenia during the past twenty years, in a total of 145 patients seen at the Neurological Clinic of the São Paulo Medical School. In spite of the fact that myasthenia gravis does not show hereditary characteristics, the peculiar features of the four cases justify the present report. The two pairs of siblings were born from non myasthenic nor consanguineous parents. The disease started at birth showing bilateral partial eyelid ptosis in all patients. The course of the illness has been favorable. There was no thymoma.

RESUMO

Miastenia grave familiar. Registro de quatro casos

Os autores registram dois pares de gêmeos com miastenia grave, pertencentes a duas famílias diferentes. Este é o único registro de miastenia familiar durante os últimos 20 anos, num total de 145 pacientes examinados na Clínica Neurológica da FMUSP. Apesar do fato de a miastenia grave não ter características hereditárias, os aspectos peculiares dos quatro pacientes justificam o presente registro. Os dois pares de gêmeos nasceram de pais não miastênicos e sem consanguinidade. A doença iniciou-se no nascimento, evoluindo com ptose bilateral parcial da pálpebra superior precocemente em todos os pacientes. O curso da moléstia tem sido favorável. Não havia timoma.

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