PELIZAEUS-MERZBACHER DISEASE: ELECTROPHYSIOLOGICAL STUDY OF TWO SIBS WITH THE CLASSIC FORM AND OF THEIR RELATIVES

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We examined two sibs with the classic form of Pelizaeus-Merzbacher disease (PMD) and their relatives. Electromyographic-electroneurographic studies and magnetic stimulation of motor pathways were performed. In both patients we found an absence of compound motor action potential (cMAP) after stimulation of the motor cortex and a normal conduction time by stimulating the cervical roots. Despite reported sparing of the peripheral nervous system in PMD, our conduction study of the tibial nerve revealed a slightly decreased motor nerve conduction velocity in one patient. In both patients the EMG study showed neurogenic findings. The elder sister showed a prolonged central motor conduction time. This study demonstrates abnormalities of motor corticospinal pathways also in PMD relatives suggesting that magnetic stimulation could be useful in detecting "subclinical" abnormalities in this dysmyelinating condition. Furthermore, in accordance with previous studies, we suggest that a slight involvement of the peripheral nervous system could be observed in PMD.

KEY WORDS: Magnetic stimulation of motor pathways, Pelizaeus-Merzbacher disease, peripheral nerve conduction.

INTRODUCTION

In 1885 Pelizaeus described a family with an X-linked dysmyelinating disorder that extended over a number of generations, and in 1910 Merzbacher examined the brain of an affected individual from the same kindred (1,2). The neuropathological appearance was characterised by a marked deficiency of central nervous system (CNS) myelin; oligodendrocytes were reduced in number, while axons were preserved, except for a reduction in the pyramidal ones. Myelin appeared normal in the peripheral nerves (2). On the basis of progressive myelin degeneration in the brain, Seitelberger classified the disease as a leukodystrophy and, in 1970, proposed a classification based on clinical findings (in particular, age at onset and at death), pattern of demyelination, pattern of inheritance and neurochemical findings (3).

Typically, Pelizaeus-Merzbacher disease (PMD) has its onset in infancy or early childhood. The most consistent initial clinical features have been found to be nystagmus, head titubation, jerky movements of the head or
limbs, and inspiratory stridor. The infants are usually floppy early on and regression of whatever initial psychomotor development has been attained dates from 3 months onwards.

Speech typically does not develop and patients are unable to walk (3,4). Choreoathetosis is a common clinical finding. The disease often progresses, leading to death in late adolescence or young adulthood, although there are patients who survived until the sixth decade (1,4).

MRI shows hypomyelination or absence of myelin, with an increased signal on T2-weighted images (5,6). Electrophysiological studies in patients with PMD have revealed abnormalities in somatosensory, acoustic and visual evoked responses (7-9). Only in a few cases has magnetic stimulation been performed in order to ascertain the functional integrity of corticospinal tracts in PMD (10). The aim of this study was to consider the role of the electrophysiological investigations of central motor pathways and peripheral nerves in patients with PMD, and in their relatives.

MATERIALS AND METHODS

Two male sibs with the classic form of PMD were investigated. They underwent complete neurological examination, EEG, and neuroradiological investigations (brain CT scan and MRI). EMG study of the tibialis anterior muscle, motor nerve conduction study of the tibial, deep peroneal and median nerves, sensory nerve conduction study of the sural and median nerve, and conduction study of the central and peripheral motor pathways using magnetic stimulation were carried out in the two patients. Their parents and their two sisters underwent the same electrophysiological investigations, except for the peroneal motor nerve conduction study. The skin temperature over the recording muscles was maintained between 32 and 34°C using a thermistor connected to an infrared lamp.

Magnetic stimulation of motor pathways

Informed consent was obtained from each subject (from the parents in the case of the two children). The subjects were examined in supine position. A Novametrics Magstim 200 stimulator was used to generate a magnetic field of up to 1.5 Tesla (T), pulsed for 100 µsec into a copper coil (inner diameter 9 cm). The magnetic field-inducing pulse wave was bipolar. The stimulating coil was held tangential to the scalp and positioned over the vertex (Cz); current flow direction was clockwise when stimulating the left hemisphere and anticlockwise when stimulating the right hemisphere. The same device was used for stimulation of the cervical spinal roots in order to obtain an estimation of the peripheral conduction time to the muscle also examined by cortical stimulation. The stimulating coil was placed over the spinous process of the seventh cervical vertebra. At least four stimuli were delivered to the scalp and to the cervical region to ensure the repeatability of the observed response. Surface recording electrodes (Dantec 13L20) were placed over the abductor pollicis brevis (APB) muscle. Since the level of muscle activation influences the latency, the amplitude and the threshold of the compound motor action potential (cMAP) obtained by motor cortex stimulation (11), the stimuli were delivered in two different conditions: 1) when the subjects were quiet and the recording muscle was relaxed (absence of preinnervational muscle activity was demonstrated by EMG silence during 20 ms prior to the stimulus artifact), and 2) during a slight contraction of the APB muscle obtained in response to a strong exteroceptive stimulus delivered to the palm in the patients, and through voluntary contraction (about 20% of the maximum voluntary contraction) in their relatives. Latency and amplitude of the cMAPs were recorded following a magnetic stimulus of 1.5T intensity. To exclude a proxi-
normal involvement of the spinal roots, the shortest latency of 10 F waves obtained following stimulation of the median nerve at the wrist was considered and central motor conduction time (CMCT) was calculated, according to Robinson et al. (12), using the following formula:

$$CMCT = TMCT - [(F + M - 1)/2]$$

in which TMCT is the total motor conduction time, F is the shortest latency of 10 F waves, M is the motor distal latency after stimulation of the median nerve at the wrist and 1 (1 msec) is the estimated turnaround time delay of the antidromic volley at the anterior horn cell. As previously demonstrated, maturation of corticospinal tracts is slower than that of sensory and peripheral motor nerves and the F wave latency presents specific age-related values (13). Therefore, in accordance with previous studies (14,15), differences in body size and age-dependent changes in measurements were taken into account. Peripheral motor conduction time (PMCT) was normalised to arm length, the latter being defined as the distance between the seventh cervical vertebra and the surface electrode over the thenar eminence (normalised values: msec/m) (14). F wave measurements and motor conduction values obtained by magnetic stimulation were compared to those of normal subjects considered in the following age groups: 9-10 yrs (no.=7), 11-13 yrs (no.=9) and 14-18 yrs (no.=15) [no. = number of normal children in each age group]. PMCT values obtained from the patients’ parents and two sisters were compared with the standard parameters used by our laboratory for adult subjects in the normal height range. EMG recordings with bandpass range between 10 Hz and 2 kHz were obtained using a Mystro-Medelec electromyograph. Single electrophysiological parameters outside ± 2.5 SD of the mean normal value for PMCT and ± 3 SD for CMCT, were considered abnormal.

CASE REPORTS

Case 1

Patient 1 is the third child of unrelated parents. He was born at term by normal vaginal delivery weighing 3.44 kg and was considered normal in the neonatal period. He was first referred to us at 8 months. Weight was 7.65 kg, length 72 cm and head circumference 44 cm. On examination he had no dysmorphic features and there were no indications of metabolic disorders. His developmental level was assessed as less than three months. He had no head control, hypertonic lower and upper limbs with symmetric hyperreflexia contrasting with marked truncal hypotonia. He had extreme difficulty with feeding having developed problems with sucking and swallowing, and he was failing to thrive. He smiled spontaneously, his visual fixation and following were normal. Routine blood tests, karyotype, CSF and lysosomal enzyme studies were normal. TORCH infections were excluded. Oligosaccharide, mucopolysaccharide and amino acid excretion patterns in the urine were normal. Fundus oculi was normal. EEG showed slow rhythm in the occipital areas. At that time cerebral palsy was suspected. At 3 years he developed seizures and generalised severe hypotonia. Pendular nystagmus and convergent strabismus were present at 4 years. He had no bowel or bladder control. Speech was limited to vocalisation. Brain CT scan showed slight atrophy of the frontal lobes and ventricular enlargement. When he was 3 years old his brother (case 2) was born and presented with severe psychomotor delay in the first year of life. The possible diagnosis of cerebral palsy in patient 1 was, at this point, doubted. Muscle biopsy of the quadriceps femoris was performed in both patients. In patient 1 it showed muscle tissue made up almost exclusively of type II fibres. The histochemical study revealed a generalised, moderate COX deficit. No pathological
changes were observed in patient 2. MRI performed at age 9 in patient 1 showed, in T2-weighted images, symmetrical areas of hypomyelination with a high-intensity signal involving the white matter of the cerebellum, of the periventricular frontal regions, and of the cerebral lobes, with no involvement of the brainstem (Fig. 1). Pelizaeus-Merzbacher disease (classic form) was then diagnosed.

Case 2

The brother of patient 1 was born at term after an uneventful pregnancy and delivery, weighing 3.63 kg. He was first referred to us at 5 months. Weight was 7.12 kg, length 68 cm and head circumference 43 cm. He was severely retarded, his developmental level being assessed as two months. He was barely alert, visually inattentive, had no head control and could not grasp toys. On examination he had hypoplastic maxillae, proximal hypertonia of the limbs with symmetrical hyperreflexia and marked truncal hypotonia. The Moro reflex was still present. TORCH investigations were negative. Karyotype, metabolic investigations, CSF, EEG, and fundus oculi were normal. Brain CT scan showed slight atrophy of the frontal lobes. At 30 months convergent strabismus and nystagmus appeared. Six months later clonic twitching of eyelids and mouth with tonic deviation of the arms occurred. These seizures were recurrent and were sometimes accompanied by apnoeic spells. At the age of 4 he developed severe generalised hypotonia and muscle weakness. Jerky movements of the lower limbs frequently occurred with ankle clonus. Deep tendon reflexes were increased with clonus. He had a startle reaction to loud noise. Involuntary sucking and chewing movements and difficulty with swallowing were present. Speech was limited to vocalisation. MRI showed ventricular enlargement, minimal cortical atrophy, and reversal of white matter signal intensity on T2-weighted images with a symmetrical patchy pattern of hypomyelination in the periventricular frontal regions and in the cerebellar hemispheres (Fig.s 2 and 3). Pelizaeus-Merzbacher disease (classic form) was then diagnosed.

RESULTS

Table I summarises the data obtained through the magnetic stimulation of the motor pathways in the two patients and in their relatives. In both patients we found no cMAP after

Fig. 1 - MRI in T2-weighted images showing symmetrical areas of white matter hypomyelination of the periventricular frontal regions and of the cerebral lobes. (Case 1)

Fig. 2 - MRI in T2-weighted images showing ventricular enlargement and symmetrical patchy pattern of hypomyelination in periventricular frontal regions. (Case 2)
stimulation of the motor cortex (Table I and Fig. 4, see over). This was the case both during complete relaxation and with slight contraction of the APB muscle. In contrast, it was possible to elicit cMAP by stimulating the cervical roots at the level of the seventh cervical vertebra. In both patients the PMCT normalised to arm length was within the normal range (Table I and Fig. 4). The shortest F wave latency value, obtained through stimulation of the median nerve at the wrist, was normal in all the subjects examined. The patients’ parents and the younger of their two sisters showed a normal CMCT, whereas the elder sister showed a prolonged CMCT.

Neurological examination was normal in all the patients’ relatives.

Motor conduction study of the median nerve (elbow to wrist) revealed normal motor nerve conduction velocity (MNCV) values, distal motor latency and cMAP amplitude in all the subjects examined. Motor conduction study of the tibial nerve (knee to ankle) revealed a slightly decreased MNCV in the older patient (37.3 m/s in the right side, 37.1 in the left side; normal lower limit value: 40.6 m/s) while their distal motor latency and cMAP amplitude were normal. In the rest of the family members, these parameters were within the normal range.

The EMG study of the tibialis anterior muscle using a co-axial needle electrode demonstrated, in both patients, neurogenic findings characterised by spontaneous activity (i.e., fibrillations and positive sharp waves), by increased duration and amplitude of motor unit potentials and by an augmented number of polyphasic shapes. This investigation did not reveal any abnormalities in the other family members examined.

In both patients, motor conduction study of the deep peroneal nerve was normal. The sensory conduction study of median and sural nerves (orthodromic conduction II digit-wrist in the median nerve and antidromic conduction in the sural nerve) were normal in all the subjects examined.

Table 1 - Magnetic stimulation of motor pathways (recording from abductor pollicis brevis muscle).

<table>
<thead>
<tr>
<th>Age yrs</th>
<th>CMCT° ms</th>
<th>PMCT* ms/m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>12</td>
<td>Cortical cMAP absent</td>
</tr>
<tr>
<td>Patient 2</td>
<td>9</td>
<td>Cortical cMAP absent</td>
</tr>
<tr>
<td>Mother</td>
<td>39</td>
<td>6.0 (4.3±2.4)§</td>
</tr>
<tr>
<td>Father</td>
<td>41</td>
<td>6.2 (4.3±2.4)§</td>
</tr>
<tr>
<td>Older sister</td>
<td>21</td>
<td>7.9 (4.3±2.4)§</td>
</tr>
<tr>
<td>Younger sister</td>
<td>20</td>
<td>6.6 (4.3±2.4)§</td>
</tr>
</tbody>
</table>

Abbreviations: CMCT = central motor conduction time; PMCT = peripheral motor conduction time.
* By using Robinson and co-workers’ formula. * Normalised value for age and upper limb length, (§) Mean values ± 3.0 SD from normal subjects, (≠) Mean values ± 2.5 SD from normal subjects. Bold values are abnormal.
DISCUSSION

Pelizaeus-Merzbacher disease is an X-linked leukodystrophy characterised by nystagmus, ataxia, choreoathetosis, spasticity, and mental deterioration. In 1970, Seitelberger proposed a classification based on clinical findings, pattern of demyelination, pattern of inheritance, and neurochemical findings. He identified six types. The major problem with this classification is that it groups a number of dysmyelinating conditions under the heading PMD in spite of their genetic heterogeneity, thus confusing the nosology of the disease originally described by Pelizaeus-Merzbacher (4). The definition of PMD should be restricted exclusively to the first two types included in Seitelberger’s classification: classic form (type I) and connatal form (type II). The classic form can be distinguished from the connatal form primarily on the basis of rate of progression (less rapid than in connatal cases), age at death

Fig. 4 - Magnetic stimulation of motor pathways in both sibs (Case 1 and Case 2) with PMD. Absence of cMAP following stimulation of motor cortex during muscle relaxation (A) and muscle activation induced by skin stimulation of the palm (B). PMCT obtained by spinal root stimulation at C7 level is normal in both patients (C). Electrophysiological parameters: 10 ms/div, 0.5 mV/div.
ond decade in classic cases versus first decade in connatal cases), and severity of the neuropathology (partial demyelination with a tigroid appearance in classic cases versus total demyelination in connatal cases). In the connatal cases both X-linked recessive and autosomal recessive inheritance have been reported, while in the classic form inheritance is X-linked recessive (16). In the X-linked disease, the defect involves the gene on the X-chromosome encoding proteolipid protein (PLP), a crucial structural protein of myelin (17).

We studied two brothers with the classic form of Pelizaeus-Merzbacher disease. The diagnosis was based on clinical features of nystagmus and progressive encephalopathy, and on MRI findings. In fact, our MRI study of the two brothers revealed a marked reduction in the white matter. Symmetrical areas of hypomyelination involving the white matter of the cerebellum and of the periventricular regions were present on T2-weighted images. There was no involvement of the brainstem.

In this study we observed a clear involvement of the central motor pathways in two sibs with Pelizaeus-Merzbacher leukodystrophy.

In both patients EMG recording from the APB following magnetic stimulation demonstrated absence of cMAP when stimuli of maximal intensity were delivered to the scalp, while normal latencies were obtained following stimulation of the cervical roots.

Our findings are in general agreement with a previous electrophysiological study (10). However, in that study the clinical aspects of the patients diagnosed as having PMD were not sufficiently described, neither were the electrophysiological parameters of motor nerve conduction obtained by magnetic stimulation of the spinal roots adequately evaluated. In fact, the author did not perform the F-wave study which would have allowed exploration of the intraforaminal tract of the motor cervical roots. Finally the need to normalise the PMCT to the arm length was not considered. The PMCT is subject to rapid variations in relation to the body size changes that occur in childhood, i.e. within the age range of our patients (14,15).

An interesting aspect emerged from the electrophysiological investigation carried out in our patients’ relatives: the elder of the patients’ two sisters showed an increased CMCT. This alteration must be considered subclinical, as the neurological examination of this subject did not reveal any abnormalities.

The finding of central motor abnormalities in female relatives of patients with PMD could be important in the identification of ‘electrophysiological markers’, themselves expressing possible genetic abnormalities responsible for the disease. It would be useful at this point to carry out a genetic study of all the family members in order to confirm this hypothesis.

What emerges from our study is that transcranial magnetic stimulation of the motor pathways could provide an investigative tool for documenting dysmyelinating conditions and could also be useful in the detection of leukodystrophies with early pyramidal signs. Several studies have outlined the absence of peripheral nervous system involvement in PMD (2-4). This has, in fact, been one of the clinical criteria for the diagnosis of this type of leukodystrophy. However, some studies have recently obtained neurogenic findings resembling a spinal muscular atrophy (18) and mild slowing in MNCV in some patients with PMD (19). Our study has also shown that peripheral nervous system involvement can be present in PMD and it could affect primarily the motor axons. In fact, we observed a slight decrease in the MNCV of the tibial nerve in one patient, and in both patients the EMG study of the tibialis anterior muscle produced neurogenic findings. Since the motor conduction of the deep peroneal nerve was normal, we were able to exclude, in both patients, focal neuropathies of this nerve, in particular those related to mechanical compression at the head of the fibula.

The mechanisms responsible for these pe-
Peripheral nervous system abnormalities still remain to be clarified. The characteristics of the electrophysiological damage found in our investigations (only slight decrease in MNCV and neurogenic findings from the EMG study) could favour the hypothesis of primarily axonal damage of the peripheral motor nervous fibres. An observation analogous to ours, that is, peripheral neurogenic damage limited to the motor axons, was recently reported by Kaye et al. in two brothers with PMD (18). They hypothesise two possible mechanisms: 1) the genic product of the PLP could provoke an alteration in the development of the anterior horns of the spinal cord; 2) the genic product of the PLP could cause a dysmyelinogenesis of the peripheral nervous system. Our electrophysiological findings, together with those of the aforementioned researchers, favour the first of the two hypotheses in so far as significant slowings of peripheral nerve conduction compatible with myelinopathy were not observed. Our study has, in any case, highlighted an important difference between the involvement of the central and peripheral motor pathways, in that severe damage of the corticospinal tracts is associated with a mild alteration of the peripheral motor pathways. This suggests that the progression over time of PMD could determine a rostrocaudal degeneration of the motor pathways.

Therefore, it could be hypothesised that the involvement of the peripheral motor nerves in PMD depends on transneuronal degeneration of the α-motoneuron consequent to pyramidal tract lesions (20,21). The same phenomenon has been proposed to explain the neurogenic findings observed in the striated muscles of hemiplegic subjects (21,22) and the slight slowing of peripheral nerve motor conduction found in hemiplegia (22). However, while selective atrophy of type 2 fibres together with an increase in type 1 fibres has been observed in hemiplegia (23-25), we found an almost exclusive presence of type 2 fibres in case 1 and a normal distribution of type 1 and 2 fibres in case 2. This discrepancy renders the transneuronal degeneration hypothesis rather unlikely.

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