SHORT REPORT

Congenital oculo-bulbar palsy

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Abstract

A girl developed progressive weakness of bulbar and ocular muscles starting before the age of two years. Electromyography revealed a widespread subclinical myopathy. An intercostal muscle biopsy showed complex abnormalities including occasional neurofilamentous accumulations and honeycomb-like membranous material in terminal axons. Endplates were small and some secondary synaptic clefts were abnormally deep. Acetylcholine receptors extended unusually deeply into the clefts of the junctional folds. Muscle fibres showed subsarcolemmal vacuolation at some places. This form of congenital oculo-bulbar palsy does not appear to have been described previously.

Selective weakness of ocular and bulbar muscles in early infancy is rare and in most cases due to congenital myasthenia or myasthenia gravis.^{1,2} Ocular muscle weakness may accompany bulbar palsy in Fazio Londe disease³ and progressive oculo-bulbar weakness with peripheral neuropathy and evidence of corticospinal tract involvement has been described in one infant with giant axonal neuropathy (GAN).⁴ Weakness of ocular and bulbar muscles is a feature of several congenital myopathies but is associated from the onset with weakness of limb muscles.⁵

Our case does not appear to have been reported previously. It is characterised by: 1) Onset before the age of two years; 2) Oculo-bulbar weakness; 3) Subclinical involvement of the trunk and limb muscles and 4) Lack of obvious progression. An extensive investigation revealed a series of abnormalities at neuromuscular junctions, distal axons and muscle fibres.

Case report

This girl was the eldest of three siblings, children of unrelated, healthy, young parents. Pregnancy, delivery and psychomotor development were described by the parents as normal. When asked, the parents agreed that the child had probably never laughed. At the age of two years, ptosis was diagnosed by an ophthalmologist. Neurological examination at the age of four years disclosed bilateral ptosis and limitation of abduction of the eyes. Smiling was feeble and speech was nasal in tone. At nine years, voluntary and reflex eye movements

were restricted in all directions. She could not inflate her cheeks nor raise the corners of her mouth. Speech had not obviously changed. Examination of the limbs and trunk revealed no abnormalities. At 11 years, her condition was unchanged.

Laboratory examination at the age of five years showed that serum CK activity was not raised and that there were no antibodies to acetylcholine receptors (AChRs). CT scans of the mediastinum and brain were normal. Concentric needle EMG provided no evidence of denervation. The motor unit potentials in the frontalis muscle were abnormally prolonged. Motor nerve conduction velocity was normal. Stimulation of ulnar and facial nerves at frequencies of 2, 3 and 10 Hz did not result in decrement of the muscle action potentials. A double response to a single stimulus was not seen. Single fibre (SF) EMG of the orbicularis oculi muscle was performed at five years of age and the findings were confirmed at nine years. At the latter examination, jitter of up to 174 μ s were measured. Mean consecutive difference (MCD) for 22 fibre pairs was 57 μ s. Blocking was observed in 8 of 22 fibre pairs. Abnormal jitter but no blocking was seen in the extensor digitorum communis dexter muscle. Treatment with pyridostigmine bromide was unsuccessful.

Material and methods

Parental consent was obtained to carry out a biopsy of the external intercostal muscle under general anaesthesia. Control intercostal muscle was obtained during thoracotomy from two four year old patients who did not suffer from neuromuscular disorders.

For a detailed description of the methods used we refer to another recent publication.⁶ All recordings during in vitro electrophysiology were made at 20–22°C. Miniature endplate potentials (Mepps) were corrected for standard resting potential of –80 mV. All values are means (SE). Transverse cryostat sections were used for routine histological and histochemical stainings of muscle fibres. Intramuscular nerves and endplates were stained according to the method by Pestronk and Drachman.⁷ Camera lucida drawings of endplates and innervating axons were made at $\times 1000$ magnification and used for quantitative investigations. Acetylcholine receptors were demonstrated at the light microscopical and ultrastructural level using rat monoclonal

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Figure 1 Electron micrograph. A) Neurofilamentous axonal swelling in non-myelinated intramuscular nerve fibre. For comparison, note the contracted sarcomeres in the muscle fibre at the bottom. B) Detail, showing mal-orientation of neurofilaments. Bar = 1 μ m.

antibody 35 (mcAb 35), directed against the main immunogenic region (MIR) of the alpha subunit of AChR.⁸ Ultrathin sections of Epon embedded material containing endplate regions were contrasted with uranyl acetate followed by lead citrate. Neuromuscular junctions (NMJs) were viewed under the electron microscope and photographed at a final magnification of $\times 18\,000$. Quantitative investigations were performed on electron-micrographs using a digitiser attached to an IBM-PC and included the number of nerve terminals per muscle fibre, nerve terminal areas, presynaptic membrane lengths, deepest secondary synaptic cleft per NMJ and per case and diameter of synaptic vesicles. Statistical evaluations were performed with the Mann Whitney U test two sided.

Results

Microelectrode studies revealed a mean (SE) resting membrane potential of -66 mV (1.9). Mepps were normal in shape. Their mean (SE) amplitude was 1.3 mV (0.144) (9 endplate approximately 20 Mepps per endplate). Endplate potentials could not be measured due to lack of bundles in the biopsy containing a suitable piece of nerve for stimulation.

Light microscopy Transverse cryostat sections showed an occasional atrophic fibre and a mosaic pattern of type I and II fibres. Myelinated intramuscular nerve fibres appeared normal. The diameter of 500 of these fibres (measured in toluidine blue stained one μ m Epon sections) varied from 1.5 – 5.5 , the histogram showing a single peak at 2 μ m. This was all within the normal range.⁹ Preterminal axons in silver cholinesterase stained cryostat sections appeared normal. Collateral branches innervating other muscle fibres were seen rarely as in control muscles. One of 50 fibres had two endplates, as in age matched controls. The length of 50 cholinesterase stained endplates was measured "blind" in the patient and in the controls and was slightly less in the patient (19.1 μ m, SD 5.95 v 22.2 , SD 5.02 and 22.5 , SD 6.24 ; $p < 0.01$). Staining of AChRs was unremarkable.

Electron microscopy In one section, 3 enlarged non-myelinated axons measuring up to 12 μ m in diameter were discovered in between the muscle fibres (fig 1). These axons were packed with neurofilaments, some of which were wrongly orientated, crossing other neurofilaments transversely. No enlarged axons were seen in any of the other sections. Some non-myelinated preterminal axons contained honeycomb-like membranous material. The number of nerve terminals per endplate was less than in controls (1.23 , SD 0.4 , $n = 31$; versus 2.00 , SD 1.0 , $n = 13$ and 1.66 , SD 0.8 , $n = 38$; $p < 0.02$). Nerve terminals were unremarkable and synaptic vesicles had normal diameters. The presynaptic membrane length was within the normal range. The nerve terminals were often covered by several processes of Schwann cells, something which was not seen in controls. Multiple processes and nuclei of Schwann cells and many layers of

Figure 2 Electron micrograph of a faintly contrasted section. Acetylcholine receptors are visualised using a two-step immunoperoxidase method. Secondary clefts can be seen clearly. Staining of receptors is seen as an unbroken line along the primary cleft, at the top of the secondary clefts and at many sites deep down in the clefts. Bar = 1 μ m.

basal membrane were often in the immediate vicinity. Schwann cell processes were seen to intrude frequently into the primary synaptic clefts. Some of the secondary synaptic clefts were abnormally deep and variable in shape (deepest secondary cleft in the patient was $7.36\ \mu\text{m}$, in controls 2.81 and 3.10). AChRs were present not only at the top of the folds but sometimes along the entire length of the secondary clefts or deep down in the clefts (fig 2). In the muscle fibres, myelinoid material and vacuolar spaces were occasionally present in the subsarcolemma.

Discussion

Weakness of ocular and bulbar muscles and lack of obvious progress were the main clinical features of the syndrome described above. The results of EMG were compatible with a widespread disorder of terminal motor nerve fibres or neuromuscular junctions. In vitro electrophysiology showed that Mepps were not decreased in amplitude which precluded deficiency of AChRs. A disorder of transmitter release could not be ruled out.

The histological investigations revealed a striking array of pathological changes. The abnormal depths and variable shape of some of the secondary clefts and the presence of AChRs deep down in the clefts were indicative of a developmental disorder. The area of contact between muscle and nerve was decreased, compared with controls and other data collected in our laboratory.¹⁰ This decrease was due to a reduction in the number of nerve terminals per endplate and intrusion of Schwann cell processes into the primary synaptic clefts. A decrease in contact between nerve and muscle has been observed when the effect of the neurotransmitter acetylcholine is excessive as in cholinesterase deficiency or in the slow channel syndrome.^{2,6} Another abnormality was the increase in the number of Schwann cell processes covering the terminals, and of Schwann cell nuclei and processes near nerve terminals. An increase of Schwann cells is seen in de- and remyelinating conditions and in Wallerian degeneration. Such an increase near neuromuscular junctions can best be

explained by instability of contact between nerve and muscle: retraction or degeneration of nerve terminals and re-establishment of contact by the same or another nerve terminal. Subsarcolemmal vacuolisation in muscle is a secondary change of a degenerative nature and suggests dysfunction of the muscle membrane. Neurofilamentous axonal swellings have been related to axonal transport disorders and have been observed in GAN, neuroaxonal dystrophy and toxic neuropathies.¹¹

Congenital non-progressive oculo-bulbar palsy as described here is the clinical expression of a disorder which affects the musculature widely. Underlying this syndrome are a series of changes in distal axons, neuromuscular junctions and muscle fibres. The disorder should be included in the differential diagnosis of patients presenting with weakness of ocular and bulbar muscles in infancy.

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