Asymptomatic benign familial spinal muscular atrophy with hypertrophy of the calves and high creatine kinase levels

Sir: In spinal muscular atrophies, hypertrophy of the calves \(^1\)–\(^4\) and an increase of serum creatine kinase (CK) activity \(^2\)–\(^5\)–\(^6\)–\(^8\)–\(^9\) have been found. We report an asymptomatic 33yearold man, with only hypertrophy of the calves and high blood level of CK. Further investigations indicate that the patient had benign familial spinal muscular atrophy.

The proband was a 33yearold Japanese man. The family history was negative for neuromuscular disorders. At the age of 32 years, raised serum CK activity (762 U/l) (normal: 25–170) was noted incidentally. He visited our clinic at the age of 33 years because of the raised CK level. There was gross hypertrophy of the calves. No other general or neurologic abnormalities were observed. Muscle strength and tendon reflexes were normal. Routine laboratory data including erythrocyte sedimentation rate, blood cell count, and serum chemistry were normal except for serum CK, GPT, LDH, and aldolase. Serum CK activity ranged from 654 to 820 U/l (normal: 25–170), aldolase was 7.8–11.0 U/l (normal: 1.2–7.6), GPT was 66 U/l (normal: 5–47), and LDH was 202–286 U/l (normal: 125–220). Levels of GOT were within normal limits. Serum CK isozymes consisted of 0% BB type, 3% MB type, 91% MM type, and 5% albumin. There was abnormality in electrocardiogram. Serum levels of pyruvate and lactic acid were normal at rest and after exercise. Needle electromyogram (EMG) revealed decreased interference patterns and high amplitude, long duration potentials in the right deltoid, triceps brachii, extensor digitorum communis, and quadriceps femoris muscles. The high amplitude potentials were polyphasic and firing at high rates. No spontaneous activity was recorded in the EMG. Motor and sensory nerve conduction velocities were within normal limits in the upper and lower extremities. CT of the legs revealed true hypertrophy of the calf muscles. A muscle tissue was biopsied from the quadriceps femoris. The specimen was rapidly frozen in isopentane cooled in liquid nitrogen, and cryostat sections were stained by histological and histochemical methods of Dubowitz. The biopsy specimen included 840 muscle fibres. Average size of the muscle fibres was 77 \(\mu\)m. A few small angulated fibres (about 1% of all of the fibres) were scattered. Hypertrophic fibres, more than 80 \(\mu\)m in diameter, were found in 41% of the total. There was no necrotic fibre or interstitial fibrosis. No ragged red fibres were found in modified Gomori trichrome stain. The standard ATPase reaction (pH 9.4) demonstrated that all the fibres were uniformly type 2. Acid pre-incubation (pH 4.6 and 4.3) of the ATPase reaction revealed that the muscle consisted of type 2a (38%) and 2b fibres (62%). Average diameter of type 2a fibres was 81 \(\mu\)m, and that of type 2b fibres 74 \(\mu\)m. Fibre type grouping was found with clusters of both type 2a and type 2b fibres. The small fibres belonged to type 2b.

We examined the patient's father who was 61 years old. General and neurologic examinations were normal. There was no hypertrophy of the calves. The serum chemistry revealed elevated activities of CK (342 U/l), LDH (277 U/l), and aldolase (9.4 U/l). The needle EMG revealed high amplitude, long duration potentials, which were also polyphasic, in the right quadriceps femoris and extensor digitorum communis. Polyphasic, long duration potentials were found in the right deltoid, biceps brachii, and triceps brachii. No spontaneous activity was recorded in the EMG.

The proband is characterised by hypertrophy of the calves, high CK level, and abnormalities in EMG and muscle biopsy. The findings of EMG and muscle pathology suggest impairment of the lower motor neuron, which implies that the patient is asymptomatic affected with spinal muscle atrophy. In the muscle pathology, the muscle fibres consisted of only type 2 with fibre type grouping including clusters of both types 2a and 2b. Marked tendency of fibre type grouping might cause the appearance of uniform type 2 fibres in the small biopsy specimen. In the mild form of spinal muscle atrophy, large muscle fibres often show type grouping, and type 2 predominance is also common. The marked changes of the fibre types with a very few atrophic fibres found in the patient suggest that the denervating process would be chronic and be well compensated by re-innervation. Possible changes in permeability of the muscle membrane, brought by denervation and re-innervation, might cause leakage of CK, resulting in high blood levels. His asymptomatic father also showed high CK levels and neurogenic changes in EMG, although there was no hypertrophy of the calves. This suggests that both the patient and his father were affected with the same disease, benign familial spinal muscle atrophy, inherited as an autosomal dominant trait.

Asymptomatic case of SMA with calf hypertrophy and high CK levels has not been described. Autosomal dominant spinal muscle atrophy is a relatively uncommon disease. The reported cases of juvenile proximal spinal muscle atrophy inherited as an autosomal dominant trait with complete penetrance \(^2\)–\(^5\)–\(^6\)–\(^8\)–\(^9\) generally showed a benign course with slow or almost no progression in comparison with recessive spinal muscle atrophy, and some of the cases were described to present with hypertrophy of the calves \(^2\) and elevated serum CK activity. \(^2\)–\(^5\)–\(^6\) D'Alessandro et al. reported a father and son having benign spinal muscle atrophy with muscle cramps, hypertrophy of the calves, and no loss of muscle strength. In their familial cases with autosomal dominant inheritance, deep reflexes were diminished, and serum CK levels were normal.

The patient may be completely asymptomatic throughout his life because his father who is probably affected with the same disease remains asymptomatic in the seventh decade. A possibility cannot be ruled out that muscle weakness may appear later. The clinical spectrum must be further investigated in such spinal muscle atrophy variants as our cases. This spinal muscle atrophy variant would be often clinically undetected because the patients have no complaints. Investigations of these asymptomatic cases are important for elucidating mechanisms of the onset and of the disease progression in motor neuron disease.

The authors acknowledge the technical assistance of Mrs Arai.

MASAHIITO YAMADA
MISAO KANO
KYOKO CHIDA
TETSUO FURUKAWA
HIROSHI TSUKAGOSHI
Department of Neurology,
Faculty of Medicine,
Tokyo Medical and Dental University,
1-5-45 Yushima, Bunkyo-ku,
Tokyo 113, Japan

References
Reversible ataxia following chronic exposure to paradichlorobenzene

Sir: Paradichlorobenzene (PDCB) is mainly used as a moth repellent, mildew control agent and as a space deodorant. In spite of the broad spectrum of uses there are few reports of oral, inhalation or skin contact toxicity of this compound to man. Cataract formation, hepatic damage, anaemia, thrombocytopenia and lymphocytopenia have been reported following exposure to PDCB. However, no toxicity to the central nervous system (CNS) had been reported. We report a patient who developed cerebellar ataxia and speech disturbance following 6 years' exposure to PDCB.

A 25 year old woman was admitted to our hospital complaining of gait disturbance and dysarthria. She had been diagnosed as suffering from neurosis for 6 years. When she was 19 years old (1980) the unusual idea that there were many tics in her room occurred to her and she learned to use moth balls of PDCB in her bedclothes and pillow as well as in her wardrobes. Moreover she began to grind them into powder and scattered it everywhere in her room. She put on her underwear which had been kept in bags filled with PDCB powder. Her mother says that there had been a strong odour of PDCB in her room for the last few years. In January 1986, clumsiness of both hands became apparent. She could not use chopsticks. She also found difficulty in gait and speech. Gradually her signs and symptoms became worse and she could not stand without support after 2 months. There was no fever. She was admitted to a hospital where neurological examination revealed severe cerebellar ataxia, dysarthria, moderate weakness of all limbs and hyporeflexia. Computed tomography of the brain, four vessel angiography and CSF findings were normal. Her symptoms and signs gradually improved after admission. A month later she was admitted to our hospital for further evaluation.

She was alert and well-nourished; neurological examination revealed moderate limb and truncal ataxia, dysarthria, hyporeflexia, hypotonia and mild proximal weakness of the four limbs. Blood pressure was 120/80 mmHg with normal cardiac rhythm and there was no orthostatic hypotension. Normal laboratory data included blood count, electrolytes, liver and kidney function, serum creatine kinase, fast blood glucose, lactate, pyruvate, serologic reaction for syphilis and SLE, and thyroid function. Serum antibody titres to herpes, mumps, ECHO, varicella, Coackie, polio, influenza, mycoplasma and EB virus were within normal limits. CSF findings were normal and oligoclonal bands were not detected. CSF culture and stains for bacteria including anti-fast bacilli and fungi were negative. Magnetic resonance imaging of the brain was normal. EEG, nerve conduction velocity, visual evoked potentials, blink reflexes, somatosensory evoked potentials to median nerve and posterior tibial nerve stimulation were also normal. Brainstem auditory evoked potentials (BAEPs) showed a marked delay of waves III, IV and V and elongation of II-V interval while latencies of waves I and II and I-II interval were normal (fig A). Her symptoms gradually improved and became minimal in 6 months after onset. BAEPs re-examined 8 months later were normal (fig B).

PDCB is a white crystalline compound which has been used for several decades as a repellent, space deodorant and fungicide (mildew-control agent). However, toxicity to the CNS of this substance had not been reported. In our case, continuous long-term exposure for 6 years is characteristic, and inhalation and local contact are considered to be the predominant routes of exposure. In experimental animals subjected to PDCB, intense eye and nose irritation, tremors and twitches of the extremities, a “mark time” reflex, a loss of the righting reflex, a definite nystagmus, rapid but laboured respiration, reversible granulocytopenia, kidney and lung injury, and some deaths have been reported.5 6 Hollingsworth et al also observed marked tremors, weakness, loss of weight, eye irritation, unkempt appearance, and unconsciousness in rats, guinea pigs, and rabbits subjected to repeated 8-hour exposures, 5 days a week, to the high concentration of PDCB vapour. Two of the rabbits survived 62 exposures and recovered completely.7 These facts suggest toxicity of PDCB to the CNS, although the result of microscopic examination of the CNS of exposed animals was not mentioned. Reversibility of symptoms seen in the experimental models reported by Hollingsworth et al and our case may be partially attributed to rapid elimination of this substance.7 Acute cerebellar ataxia and brainstem encephalitis should be ruled out in our case. However, there was no preceding infection and no fever, speed of worsening was rather slow, and symptoms improved after cessation of exposure. Abnormalities of BAEPs have not been reported in acute cerebellar ataxia. Therefore long-term exposure of PDCB may be...
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M Yamada, M Kano, K Chida, T Furukawa and H Tsukagoshi

*J Neurol Neurosurg Psychiatry* 1988 51: 452-453
doi: 10.1136/jnnp.51.3.452

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