
LETTERS TO THE EDITOR

ALS AND MYASTHENIA: AN UNUSUAL ASSOCIATION IN A PATIENT TREATED WITH RILUZOLE

Treatment with riluzole has been proposed in both sporadic and familial amyotrophic lateral sclerosis (ALS).^{1,6,7} We report a patient with familial ALS who developed myasthenia gravis (MG) during treatment with riluzole.

A 53-year-old man, with a positive family history spanning three generations of autosomal dominant ALS, presented with weakness and atrophy in his right hand, cramping pain in the muscles of both legs, and diffuse fasciculations. The patient complained also of difficulty in walking for long distances and in arising from a chair. Clinical examination revealed hyperreflexia, muscular atrophy, fasciculations, and weakness in the arms and legs. Sensory abnormalities were not present.

Needle electromyography showed fibrillation potentials, positive sharp waves, fasciculations, and increased number of polyphasic and long-duration motor unit potentials in right tibialis anterior and vastus medialis muscles. Recruitment showed a poor interference pattern, with motor unit potentials firing rapidly. Motor conduction studies in the right and left median, ulnar, radial, and peroneal nerves were normal, as were sensory studies of the right and left median, ulnar, and sural nerves. Somatosensory evoked potentials elicited from the right and left median and posterior tibial nerves and recorded over the scalp also were normal. Motor evoked potentials had prolonged central motor conduction time (23 ms and 24 ms in right and left extensor digitorum brevis, respectively; normal value, 19 ms). Cerebrospinal fluid protein and glucose concentration and the cell count were normal.

Treatment with riluzole was started, with an initial dose of 100 mg per day. After 3 months, the patient complained of unusual muscle fatigability which was promptly reversed by rest. On examination, the patient showed ptosis and

diplopia. Repetitive nerve stimulation (RNS) at 3 Hz showed a decrement exceeding 40% in deltoid and orbicularis oculi muscle. Single-fiber electromyography (SFEMG) showed increased jitter in arms and cranial muscles (in five of 20 pairs of potentials recorded from extensor digitorum communis, biceps, and frontalis muscle, respectively) and blocks (in one of three and in three of five pairs of potentials from extensor digitorum communis and orbicularis oculi, respectively.) Following the intravenous injection of 5 mg edrophonium (Tensilon), ptosis and diplopia improved, and RNS showed a complete (biceps and deltoid) or partial (orbicularis oculi) reversal of decrement.

The serum concentration of acetylcholine receptor (AChR) antibodies was increased (22.5 pmol/L in August 1996; normal values, <0.4 pmol/L). Computed tomographic scan of the thorax was normal. Pyridostigmine bromide (Mestinon) was started at the same time riluzole was stopped, with clinical improvement, chiefly in the cranial muscles. A second SFEMG showed shortening of abnormal jitter and a decreased incidence of blocking. The serum concentration of AChR antibodies gradually decreased (4 pmol/mL in February 1997; 2.2 pmol/mL in July 1998).

In patients with ALS, electrophysiological studies often show signs of defective neuromuscular transmission^{3,8} (decrementing response to RNS, abnormal jitter, and an increased incidence of blocking), and a Tensilon test may be positive.² However, in our patient, the clinical (particularly ocular muscle involvement) and neurophysiological findings as well as the clear improvement after treatment with anticholinesterase drugs suggest a diagnosis of MG in addition to the presence of established ALS. To our knowledge, a possible association between ALS and MG is very unusual. Noseworthy et al.⁴ described a patient whose presentation suggested MG but who subsequently developed tongue fasciculations and whose lack of response to treatment led to a diagnosis of ALS. Recently, Okuyama et al.⁵ described an ALS patient with increased AChR antibody (0.50 nmol/L), but clinical features of MG were not present and the presence of the AChR antibody may simply have been a coincidental finding without any patho-

genic relevance in the illness. In contrast, the clinical symptoms of our patient and especially their localization, variability, responsiveness to anticholinesterases, and rapid disappearance make unlikely a diagnosis of motor neuron disease. We do not understand the role that riluzole—a drug that inhibits the release of glutamic acid from nerve terminals⁷—may have played in the development of MG in this subject already suffering from ALS. “Uncommon myasthenia,” not better defined, is reported as an adverse effect of riluzole by the manufacturer.⁶ We bring this rare case to attention to further elucidate the possible role riluzole may have played.

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CLINICAL IMPROVEMENT FOLLOWING INTERFERON- α ALONE AS AN INITIAL TREATMENT IN CIDP

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated disorder that usually responds to corticosteroids, intravenous gammaglobulin, or plasma exchange, but some patients are unresponsive to these treatments. Several recent reports have suggested that interferon- α (INF- α) is effective in patients with CIDP who do not respond or relapse with other therapies.^{1,2,5} We report a CIDP patient with chronic hepatitis C who showed marked clinical improvement after treatment with INF- α alone.

The patient was a 36-year-old man who had progressive

limb weakness for 6 months. He showed mild symmetric weakness of proximal and distal muscles, mild numbness in the distal limbs, and absent tendon reflexes. His grip strength was 19 kg on the right and 20 kg on the left. Cranial nerves were unaffected. Routine hematological and urine studies were normal but serum alanine transaminase (ALT) was 56 mg/dL. Immunoelectrophoresis was normal, and antiganglioside antibodies were absent. Cerebrospinal fluid (CSF) showed 5 lymphocytes/mm³ and a protein content of 779 mg/dL. Serum anti-HCV antibody and HCV-RNA were positive. Liver biopsy revealed chronic hepatitis. Nerve conduction studies showed moderately reduced motor [median nerve: distal latency (DL) 12.0 ms, conduction velocity (CV) 47.0 m/s; peroneal nerve: DL 17.4 ms, CV 29.4 m/s] and sensory (ulnar nerve CV 29.1 m/s, sural nerve CV 6.9 m/s) conduction velocities in all nerves tested. F-wave conduction velocities in the median and tibial nerves were delayed. Sural nerve biopsy showed segmental demyelination and remyelination with myelinated fiber loss, thin myelinated fibers, and small nerve clusters. Active axonal degeneration and angitis were not detected. The patient was diagnosed as having CIDP based on criteria developed by the Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force.

On the basis of the treatment protocol for chronic hepatitis C, initial treatment with INF- α (Sumiferon, Sumitomo Pharmaceuticals, Osaka, Japan) at a dosage of 9 million international units (MIU), six times per week, was initiated in September 1998. The numbness of the distal limbs began to improve 2 days after the first injection. By 1 week after the start of treatment, the sensory disturbance of his extremities had disappeared except on his soles, and his patellar tendon reflexes had returned to normal. Over the next month his muscle strength returned almost to normal. Nerve conduction studies showed improvement of conduction velocity in all nerves. After the first 4 weeks of treatment, the interferon was tapered to three injections per week. Muscle weakness continued to improve and had fully recovered by 2 months after the first injection. He had transient fever after the first several injections but no other adverse effects.

The mechanism by which interferon induced an improvement in our patient is unknown. Although the pathogenesis of CIDP is uncertain, immunohistochemical studies have shown increased expression of major histocompatibility (MHC) class II molecules on endoneurial cells.⁴ Interferons exert complex immunomodulator effects and INF- β may work by downregulating MHC class II molecule production in response to INF- γ . INF- α has a function similar to that of INF- β . The mechanism of interferon-induced improvement in CIDP is most likely related to complex immunomodulating effects exerted via reductions in the levels of proinflammatory cytokines such as INF- γ ,³ which has a role in the development of inflammatory demyelination.

INF has previously been used in CIDP after or in combination with other therapies such as corticosteroids, intravenous gammaglobulin, or plasma exchange. In our

case, it was very useful as initial therapy for improving the symptoms of CIDP.

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MUSCLE FIBER CONDUCTION VELOCITY IN arg1239his MUTATION IN HYPOKALEMIC PERIODIC PARALYSIS

The determination of the muscle fiber conduction velocity (MFCV), measured by surface⁵ as well as by invasive electromyographic methods⁴ is an important aid in confirming the diagnosis of hypokalemic periodic paralysis (hypoPP). The interictal delay in MFCV was hitherto only found in the arg528his mutation, one of three point mutations known on chromosome 1q31–32.² The MFCV with the surface as well as the invasive method showed a significant decrease in comparison to controls.⁴ The scatter of conduction velocities, expressed as the ratio between the fastest and slowest MFCV (F/S ratio), also showed an increase, due to a disproportionate conduction slowing of a part of the muscle fibers. We now confirm this characteristic electrophysiological phenomenon in a sporadic case of hypoPP with the arg1239his mutation.

A 15-year-old girl suffered from nocturnal attacks of flaccid paralysis since the age of 8 years. She was hospitalized during the first attack; serum potassium was 1.5 mmol/L. No known provocative factors were present, and family history was negative. The patient was referred to our hospital for a second opinion. The medication she used consisted of acetazolamide 125 mg twice daily, and oral potassium 20–40 mmol when symptomatic. Serum potassium was 4.3 mmol/L (normal, 3.6–4.8 mmol/L); thyrotropin stimulating hormone, 0.37 mU/mL (0.3–5.0 mU/mL); creatine kinase 25 U/L (0–50 U/L). Concentric needle electromyography of rectus femoris, iliopsoas, tibial anterior, biceps brachii, and deltoid muscle showed

no activity at rest and a mixture of normal and slightly polyphasic motor unit action potentials during volitional activation. Muscle fiber conduction velocity was measured in the left biceps brachii muscle by an invasive method as described previously.⁴ In brief, the muscle was directly stimulated by a monopolar needle electrode and a surface electrode. A small concentric needle electrode was inserted and its position adjusted until a polyphasic muscle response was found. Based on the latencies of the muscle fiber potentials and the interelectrode distance, the mean MFCV and the F/S ratio were calculated. The patient showed a decreased MFCV (2.54 m/s; normal mean, 3.07 \pm 0.21 SD) and an increased FS ratio (2.25; normal mean, 1.40 \pm 0.16 SD). Magnetic resonance imaging showed no myopathic changes. Genetic analysis revealed the arg1239his mutation on chromosome 1. The girl was the only child of two healthy parents. Only the mother could be genotyped; she did not show the arg1239his mutation.

The decreased MFCV in combination with an increase in scatter in the arg528his as well as in the arg1239his mutation suggests a common membrane abnormality and hence a common pathogenesis. The only clinical difference between both mutations is the incomplete penetrance of paralytic attacks in women with the arg528his mutation, which cannot be explained.¹

The relationship of this channelopathy to the reduced MFCV is uncertain. Measurement of the MFCV remains valuable with respect to quick diagnosis and to obtaining more insight to the pathophysiology of this disorder.³

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