LETTERS TO THE EDITOR

REPRODUCIBILITY OF CORTICOMOTOR THRESHOLD: SOME OBSERVATIONS

Recent articles by Mills et al.[2,3] raise the important question of achieving reproducible threshold (T) measurements in clinical and physiological studies. A procedure for determining threshold values was defined by an International Committee,[4] which advocates increasing stimulus intensity in 5% steps until the level T is reached which induces motor responses in about 50% of 10–20 consecutive stimuli (Method I). Mills and Nithi[2] propose an alternative procedure in which the T region is scanned in 1% steps, by using a figure eight-shaped coil, to define a lower T (LT): 0 responses in 10 stimuli, and an upper T (UT): 10 responses in 10 stimuli (Method II). The two procedures differ not only in the stepping value but also in the points where the T curve is tested. The last aspect could affect the reproducibility of T measurements if the slope of the T curve, idealized as a plot of the probability of obtaining a response versus stimulus intensity, is different at its center (where T is measured) and at its end points (where LT and UT are measured).

In order to investigate this point we measured T, LT, and UT for both abductor digiti minimi muscles on 8 healthy right-handed subjects (7 women, 27–49 years old), with their informed consent. Recordings were made with surface electrodes using a belly-tendon montage. Signals were recorded by a Keypoint EMG system (Dantec) with filters set to pass 20 Hz to 10 kHz and a sensitivity set at 100 μV/division. All measurements were carried out using steps of 5% in stimulus intensity. Biphasic stimulation was applied over the vertex with a 13-cm round coil (MagPro, Dantec) with the muscle relaxed. One investigator, who was blind to stimulus intensity, performed all stimulations and decided whether or not a response had been obtained.

Mean T values are shown in Table I. Standard deviations are similar for both methods. These spreads in T values can be ascribed to two different sources of variation: differences between subjects and variation in measurements carried out on the same subject. An estimate of the within-subject variability was obtained by analysis of variance, in the form of an estimate of the standard deviation within subjects, $(MS_{within})½$. This figure determines the reproducibility of individual measurements. The test–retest repeatability[2] is based on this figure and is also similar for both methods (see Table 1). The results show that there is no difference in reproducibility when measuring either at the end points or at the center of the threshold curve, using steps of 5%. This may be due to the large size

Table 1. Threshold measurements using the two procedures described in the text.

Methods	R.H.	L.H.	R.H. vs. L.H. *P*	Test–retest R.H.	Test–retest L.H.
Method I	53.6 ± 5.8	50.5 ± 6.0	<0.001	6.9	7.8
Method II					
Upper threshold	58.3 ± 6.6	54.6 ± 5.9	<0.001	8.8	7.3
Lower threshold	47.5 ± 6.8	43.0 ± 5.8	<0.001	8.3	7.4
Mean	52.9 ± 6.6	48.8 ± 5.7	<0.001	8.3	6.5
Method I vs. Method II (mean)	*P* = 0.210	*P* = 0.003			

Each threshold value is expressed as the mean ± standard deviation (in % of maximal output of the device) of 40 measurements: 8 subjects, five replicates per subject. Statistical analysis: Student's t*-test (paired observations), test–retest repeatability = 1.96 · (2 · MS_{within})½, in % of maximal output. R.H., right hemisphere; L.H., left hemisphere.*

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of the step relative to the LT–UT interval, approximately 11%. The test–retest figures shown here are lower than those reported by Mills and Nithil[2] presumably because, by testing each subject five times instead of twice, better estimates of the standard deviation were obtained. The use of biphasic pulses and a round coil, less sensitive to position and direction, may also have helped achieve higher reproducibility.

The mean values obtained via Method II have similar test–retest repeatability to the other single measurements. This is due to the fact that upper and lower thresholds are highly correlated ($r > 0.9$) and may represent redundant information in normal subjects.

Contrary to Mills and Nithi[2] but in agreement with others[1] we observe a significant left–right asymmetry in threshold values; a paired-observations statistical test was used since left–right measurements were carried out on the same subject on the same occasion. The small difference between the values obtained using Method I and the mean values of Method II, which reaches statistical significance in the left hemisphere, could be interpreted in terms of a small asymmetry of the threshold curve about the 50% probability point.

The question of step size and how many stimuli should be delivered at each intensity in order to optimize the amount of information obtained in an acceptable time was not addressed here. Detailed experimental knowledge of the threshold curve would be of great value in assessing this matter as well as others raised in this letter. Method I can be used reliably to study the T values in routine and research protocols.

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Reply

We are grateful to de Carvalho et al. for highlighting the importance of corticomotor threshold measurements when using transcranial magnetic stimulation (TMS). This is particularly apposite given the recent use of repetitive TMS (rTMS) and the obvious safety issues it raises. The choice of stimulus intensity in rTMS studies is usually related to resting corticomotor threshold, determined using single-pulse TMS. Clearly, an inaccurate threshold measurement could result in the parameters of rTMS exceeding safety guidelines.

de Carvalho et al. have compared two methods of measuring corticomotor threshold. The first increments stimulus intensity in 5% steps until motor responses are elicited in 50% of 10–20 trials and therefore assesses the central portion of the relationship between stimulus intensity and response probability. The second method, based on the technique we described previously but again using 5% increments, assesses the limits of this relationship, i.e., an upper threshold (UT) level giving a response probability of 1 and a lower level with a probability of zero (LT). They find no significant differences in the mean thresholds between the two methods.

Using our method with 1% increments in stimulus intensity, we found the mean (±SD) range of intensities between UT and LT to be $9.0 \pm 3.7\%$ ($n = 102$); the minimum interval between UT and LT was 3%. Thus, using Method I, it may not be possible to define threshold since a stimulus intensity of, say, 40% may yield no responses but an intensity of 45% may produce a response on every trial. Equally, using Method II with 5% increments, it may not be possible to define the stimulus intensity giving a probability of producing a response of 0.5. We would therefore argue that defining corticomotor threshold with 1% increments is preferable.

We note that de Carvalho et al. have detected a side asymmetry in threshold in their series of 8 subjects. We also note that data from five estimations in each subject were pooled in the statistics. In our series of 51 subjects, no side asymmetry emerged, although we acknowledge that small threshold differences in relation to hand preference or, more likely, hand usage may exist.

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SHOUNOUSUI AND THE BLINK REFLEX

Leon-S and colleagues compared the pattern of the electrically evoked blink reflex before and after application of a mixture named shounousui to the forehead for a maximum of 45 min in five subjects.[6] After application the R3 decreased, whereas R1 and R2 remained unchanged. The authors concluded that C fibers are the main afferent

pathways of the R3 because of a main action of capsaicin on C fibers. The topic of the study is interesting, but there are some interpretive problems.

From microelectrode studies in human nerves, it is well-known that C-fiber activity can be evoked only by transcutaneously applied electrical stimuli with intensities of 15 to 20 times the perceptual threshold.[2] This is in good accordance with studies in animals.[11] Rossi et al.,[8] however, found an electrical threshold of the R3 that was 5.5 ± 2.3 times the perceptual threshold. Unfortunately, Leon-S et al.[6] provided no information about reflex thresholds and stimulus intensities. Considering an afferent reflex arc (from the upper lid to the medullary dorsal horn) of 16 cm, it would take about 160 ms for C-fiber activity to reach the secondary sensory neuron,[3,5,7] whereas the R3 latency is about 80 ms.[4,8] Thus, the electrically evoked R3 reflex cannot be mediated by C fibers.

In their discussion, the authors equated shounousui (in unspecified concentration) with capsaicin. From topically applied capsaicin, it is well-known that it takes days before C-fiber function is affected. As shown by Simone and Ochoa,[10] the heat-pain threshold is significantly lowered 1 day following topical application of capsaicin and subsequently increases significantly above pretreatment values. The warmth threshold, another test for C-fiber function, was not significantly altered. Thus, it is very unlikely that topical application of capsaicin for 45 min decreases C-fiber function.

In summary, from this study it can not be claimed unequivocally that the R3 is a deep pain–related response. Quite the reverse, there is no evidence from this study that the R3 component is mediated by trigeminal nociceptive afferents. Possibly the modulation of the blink reflex is due to a simple focusing of attention on the electrical stimulus, which is well-known to decrease the R3.[9] It can be concluded that the neuronal circuits of the R3, nociceptive[8] or non-nociceptive,[1,3,4] are still under discussion.

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Reply

Until a few years ago, R3 of the blink reflex (BR) was considered a ''strange'' response, attracting the attention of several researchers including our group.[3,4,6,7] Dr. Ellrich disagrees with some of our interpretations on this topic.

First, he comments ''. . . C-fiber activity can be evoked only by transcutaneously applied electrical stimuli with intensities of 15 to 20 times the perceptual threshold'' and, according to him, ''This is in good accordance with studies in animals.'' This is not correct. In fact, it is possible to obtain C-reflex responses, in animals and humans, at three times to six times the pain-sensory threshold, respectively, as published in English and Spanish journals by us and others.[3–7,12]

Second, he said that ''It would take about 160 ms for C-fiber activity to reach the secondary sensory neuron,'' and that because ''the R3 latency is about 80 ms,'' the R3 is not mediated by C fibers. This is also incorrect. The latencies of the reflex responses obtained after electrical stimulation of C fibers depend on the site of stimulation.[12] Villanueva et al.[12] indicate that after application of percutaneous suprathreshold electrical stimuli, the later responses (which, according to these authors, correspond to C-fiber stimulation) occur ''in the 50–100-ms range for the cheeks, the 100–200-ms range for the forepaws, the 130–300-ms range for the proximal part of the tail, and the 300–450-ms range for the distal part of the tail.'' In monkeys there are also some long latency spike discharges, displayed usually longer than 80 ms after electrical stimulation of C fibers of the trigeminal nerve (fibers having a higher threshold and a slower conduction velocity than that observed after A-beta or A-delta stimulation).[11] Thus, there is enough evidence to state that R3 latencies certainly correspond to C fibers stimulation.[1,9]

Finally, Dr. Ellrich said that topical capsaicin ''. . . takes days before C-fiber function is affected'' making it very unlikely that ''capsaicin for 45 min decreases C-fiber function.'' Unfortunately, this is also wrong. The strongest action of capsaicin to the eye starts in between 10 and 20 min,[2] and this is in accord with our more recent results using local capsaicin (0.025% w/w) in the evaluation of R3 activity.[4]

Thus, the points raised by Dr. Ellrich are not tenable, and it can now be stated with much more confidence that

C fibers present in the human trigeminal nerve[8,10] are the afferent pathways of R3 of the BR.

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A NEW TECHNIQUE FOR PROVING NEEDLE PLACEMENT IN THE MUSCLES OF CADAVERS

Needle electromyography involves testing muscles innervated by different roots, parts of plexuses, and nerves to define the location of a specific lesion. The placement of needles accurately into the intended muscle is therefore essential.[2,3] Techniques to prove the placement of a needle have been attempted, but most have faults. Early attempts used X-ray with contrast. Jonsson used injectable radiopaque contrast material.[7] Kang used a carbon dioxide contrast X-ray to outline the muscle injected.[8] Kirchmayer calculated needle placement in paraspinal muscles using a computerized tomographic image.[9] Although such approaches can be used in vivo as well as in cadavers, the radiation, cost, indefinite outlines (especially in complex muscle groups), and inability to independently confirm placement with dissection led to their abandonment.

To our knowledge, there are only two studies that attempt to validate needle placement into anatomic specimens. We have proven the accuracy of needle location in the lumbar multifidus, longissimus, and iliocostalis muscles in a blinded protocol in cadavers by injection of red latex dye and subsequent dissection.[4] Unfortunately latex dries quickly, plugging the needle. In our study, 13% of dye pools were not found. Moreover, only a limited number of latex colors are available, so that multiple injections in multiple close sites may lead to confusion. Park et al. used India ink to prove their localization of the calcaneal nerves.[10] India ink diffuses through tissue planes, however, making it useless in muscular areas.

We have devised a technique to accurately determine both the location of the needle tip and the track which it takes through tissues. Actual written labels can be attached directly to each needle track to study multiple close insertions.

A length of 4-0 catgut suture is placed through a 20-gauge needle and bent sharply backwards at the tip, to create a hook, reminiscent of a wire electromyographic electrode used in kinesiologic studies.[1] The needle punctures the skin and muscle to the desired depth and is then carefully withdrawn, leaving the catgut in place (Fig. 1). We found that catgut works better than other more flexible suture material because it maintains its sharp angle at the edge of the needle bevel. The catgut is cut off 6–8 cm away from the skin, and a small paper label with a hole in it is placed over the catgut, which is then knotted to pre-

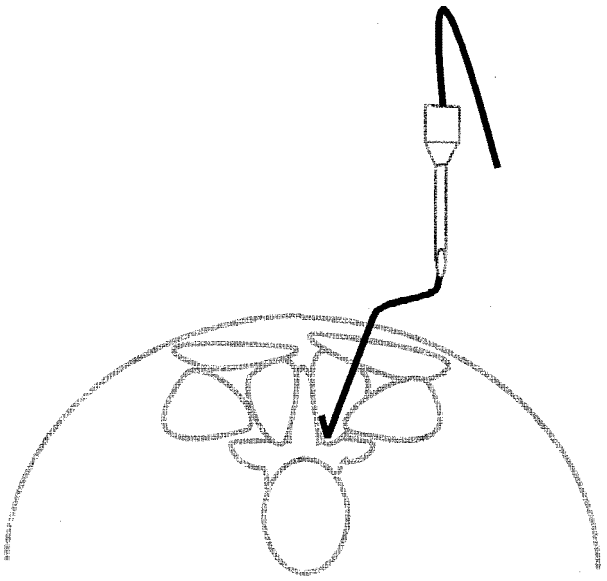

FIGURE 1. Placement of catgut suture into the tissue. After insertion into the tissue, the needle is withdrawn leaving the suture material in place. See text for further details.

vent the label from slipping off. During subsequent dissection, the catgut's course through the muscle can be determined.

We have evaluated the technique in the cervical paraspinal muscles in a single cadaver by placing two suture markers 1 cm lateral to the spinous processes of C3, C5, C7, and T2. One was directed perpendicular to the skin and the other at a 45° angle toward the midline, both being inserted until contact was established with bone. On dissection, the suture material was never found to be dislodged from the muscle layer closest to the bone.

This simple technique uses readily available materials. It permits tracking the course of the needle as well as its final resting place. Errors can be corrected by simply pulling out and reinserting the suture. Multiple locations can be labeled in close proximity without confusion.

There is a substantial benefit to validating the techniques of localizing muscles used in electrodiagnostic testing. Our previous study of the lumbar area has led to a sensitive, specific, safe, quantified, and reproducible technique for examination of the lumbar area.[5,6] Park's work resulted in the development of a method for studying conduction in a nerve that previously was not tested.[3] Even the limited data from the single cadaver presented here suggest that risk of dural puncture and pneumothorax can be minimized as a result of the more quantified approach to needle depth. For example, the data suggest that needle insertion to a depth of less than 1.8 cm beyond the muscle surface would be safe in persons the size of this cadaver, using the techniques specified.

The use of this simple technique allows for anatomic confirmation of the location of needle placement in specific muscles. Cadaver research using this technique can lead to increased accuracy and decreased harm in the needle electromyographic examination.

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RIGID SPINE SYNDROME WITH FIBER TYPE DISPROPORTION

Rigid spine syndrome (RSS) is characterized by pronounced limitation of flexion of the cervical and dorsolumbar spine, associated with scoliosis, mild proximal muscle weakness, and flexion contractures of elbows, knees, and ankles.[4] The mechanism underlying RSS is obscure. The histological findings vary from nonspecific myopathic changes to peculiar morphological abnormalities like cores,[8] rods,[12] minicores,[10] or rimmed vacuoles.[7,9] We report a case with an RSS phenotype associated with pathological findings compatible with fiber type disproportion.[3]

A 17-year-old boy presented with proximal muscle weakness and flexion limitation of the neck and trunk for 10 years. He had no history of low back pain. At the age of 9, bilateral Achilles tenotomy was performed for his bilateral pes equinus. The family history revealed first-cousin consanguinity in his grandparents. The maternal grandfather and his brother had a history of scoliosis and proximal muscle weakness.

On examination, the patient's resting posture was that of partial flexion of the trunk at the hips and extension of the neck, with thoracolumbar scoliosis. There was extreme limitation of neck and trunk flexion, with bilateral elbow flexion contractures (Fig. 1). Muscle strength testing using a modified Medical Research Council scale revealed symmetrical proximal weakness (4/5) of upper and lower extremities, with normal distal strength. The tendon reflexes were decreased. There were no other neurological abnormalities. Serum creatine kinase level was elevated at 1470 u/L (normal:30–170 u/L). Respiratory function tests, chest radiographs, electrocardiography, and echocardiography were normal. Spinal radiographs did not show any evidence of ankylosing spondylitis. Electromyography of the extremities showed myopathic changes in the proximal muscles. Nerve conduction studies were normal.

A left biceps brachii muscle biopsy showed excessive number of small type 1 fibers. Morphometric analysis of 250 fibers revealed 63% of fibers to be type 1 fibers (the expected percentage of type 1 fibers is about 42%)[6] and they were smaller than type 2 fibers (34.44 ± 13.08 μm and 89.62 ± 15.02 μm, respectively) (Fig. 2). A nonspecific esterase stain ruled out denervation. The specimens showed no central cores, rods, vacuoles, target fibers, or specific metabolite accumulations.

The mechanisms underlying RSS are not understood. It has been suggested that fibrosis and shortening of axial

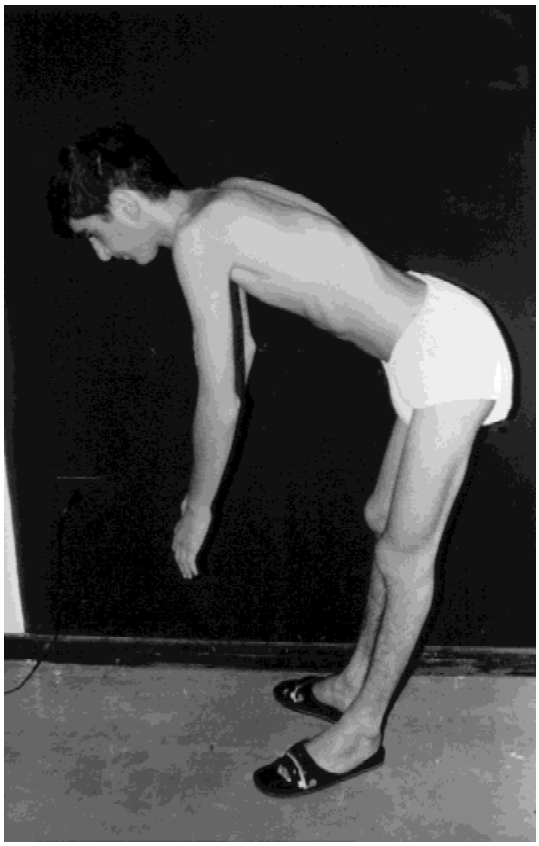

FIGURE 1. Picture of patient showing maximum capacity for flexion of trunk and neck.

extensor muscles may functionally inhibit the flexors of the spine. Alternatively weak flexors of spine may not counteract the activity of stronger extensors.[1] RSS with pathological findings of fiber type disproportion has rarely been described.[2,5,11] It is not clear whether the fiber type disproportion was due to a congenital myopathy or to a maturational defect of the motor units in this patient. A secondary histological change also bears consideration. Regardless, fiber type disproportion should be considered in the differential diagnosis of RSS.

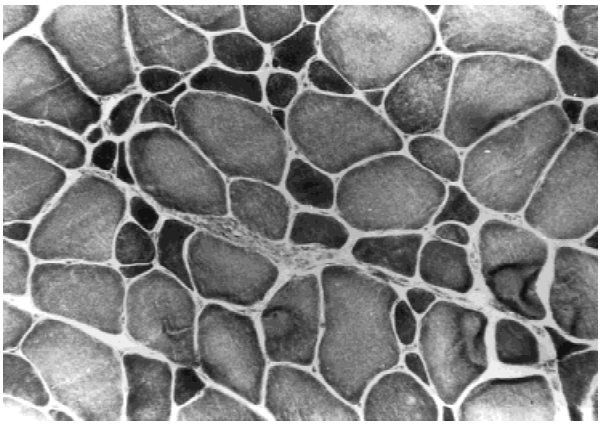

FIGURE 2. Microphotograph of biceps brachii biopsy showing type 1 fiber predominance and hypotrophy (reduced nicotinamide adenine dinucleotide tetrazolium reductase, original magnification ×70).

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SERUM IMMUNOGLOBULIN A DEFICIENCY IN RELAPSING INFLAMMATORY DEMYELINATING POLYNEUROPATHY

A girl with no family history of neuromuscular disease was 6 years old when she presented with muscle weakness, areflexia, and paresthesias in the lower limbs. A susceptibility to respiratory tract infections and diarrhea was noted. The cerebrospinal fluid (CSF) protein level was elevated (3 g/L) with cytoalbuminological dissociation. Electrophysiological studies revealed low motor conduction velocities (tibial nerve 30 m/s, peroneal nerve 31 m/s), conduction blocks (compound muscle action potential amplitude 60%

lower on proximal than distal stimulation of the right tibial nerve, without increased duration of the negative peak), and prolonged distal latencies. Neurological symptoms improved after a 5-day course of intravenous immune globulin. Clinical examination 8 weeks after initiation of treatment revealed improvement to normal of sensory and motor functions; areflexia was the only persisting abnormality in the lower limbs. A first relapse occurred 7 months later when she again developed muscle weakness, areflexia, and paresthesias in the lower limbs. Steroid therapy resulted in noticeable benefit. Force measurement was not performed, but at clinical examination 6 months after introduction of steroids, the only persisting signs were areflexia and mild distal weakness in the lower limbs. Continued treatment was deemed unnecessary and the steroids were stopped after 3 months. A second relapse occurred recently, 5 years after onset of neurological symptoms. Again, she presented with muscle weakness, areflexia, and paresthesias in the lower limbs. Steroids were not reintroduced, and neurological symptoms improved after a 5-day course of intravenous immune globulin. Two months after treatment, only areflexia persisted in the lower limbs.

The following investigations were performed during the first relapse. Serum immunoelectrophoresis revealed a severe immunoglobulin (Ig)A deficiency (<0.02 g/L; normal values: 0.5–1.68 g/L). There was also polyclonal elevation of IgG (20.3 g/L; normal values: 6.5–12.1 g/L) with no IgG subclass deficiency. Serum levels of IgM and IgE were within normal values. The serum abnormality was associated with a lymphopenia (1614 lymphocytes/mm^3; normal values: 2000–2700/mm^3) involving both B and T cells. No peripheral myelin protein-22 gene abnormality was found by molecular genetic investigations. A superficial peroneal nerve biopsy was performed, and light microscopic examination of transverse semithin sections revealed scattered fibers with excessively thin myelin sheaths. The number of myelinated fibers (MFs) was 14,076/mm^2 with a bimodal distribution. This high MF density was considered related to the moderate degree of sensory symptoms. Electron microscopic examination of transverse thin sections showed several fibers with thinned myelin sheaths and sometimes surrounded by onion bulb formations composed of Schwann cell processes (4% of MF). Moreover, 5% of myelinated fibers showed a widening of the outermost myelin lamellae (Fig. 1A). A few histiocytes were present in the endoneurium, but in spite of careful examination no evidence of active demyelination was found. Immunoblot studies revealed antibodies in the patient's serum which reacted with peripheral nervous system (PNS) proteins of different molecular weight (Fig. 1B). The most important reaction was observed with a doublet of protein bands migrating at 100/110 kDa, and which comigrated with the myelin-associated glycoprotein (MAG) as revealed by a specific anti-MAG antibody. Four other proteins showing a weaker labeling were of the size of about 82 kDa, 50 kDa , 35 kDa, and 30 kDa.

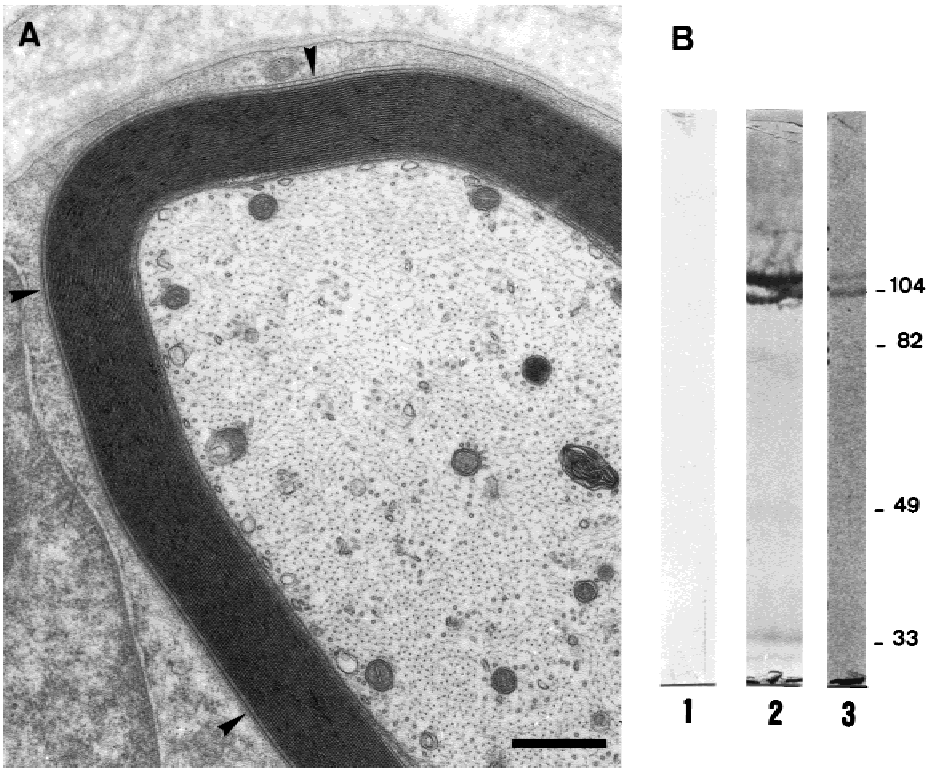

FIGURE 1. (A) Electron micrograph showing a widening of the outermost myelin lamellae (arrowheads) (bar = 0.5 µm). **(B)** Immunoblot after sodium dodecyl sulfate–polyacrylamide gel electrophoresis of rat peripheral nerve. Lane 1: serum from healthy control; lane 2: patient's serum; lane 3: specific anti-MAG antibody. Molecular mass standards are shown on the right.

Our case presented clinical and laboratory features consistent with a diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP).[3,6] IgA deficiency, which represents the most common immunodeficiency syndrome of infancy, may be associated with the presence of autoantibodies and possible development of various autoimmune diseases[1,2]; however, to our knowledge, the present case is the first reported observation of CIDP associated with IgA deficiency.

Widening of the myelin lamellae is a characteristic ultrastructural feature in polyneuropathies associated with IgM monoclonal gammopathy (MG) and anti-MAG activity.[13] A few patients with IgM MG present both widened myelin lamellae and inflammatory demyelinating lesions on their peripheral nerve biopsy,[14] thus suggesting possible overlaps between inflammatory demyelinating polyneuropathies and polyneuropathies associated with IgM MG. In the absence of IgM MG, widened myelin lamellae have been reported very occasionally in Guillain–Barré syndrome[12] or CIDP.[7,15] Although uncommon in human pathology, coexistence of widened myelin lamellae and inflammatory demyelinating lesions has been reported in experimental models.[5,8,11] Widened myelin lamellae was a surprising finding in our patient with IgA deficiency and led to a search for myelin autoantibodies.

Immunoblot studies performed with the patient's serum revealed autoantibodies recognizing several PNS proteins. The protein doublet migrating around 100/110 kDa is most probably MAG and this finding might be related to the widened myelin lamellae we observed. The protein of 35 kDa comigrates with an isoform of protein zero (P0), which has been found in a case of demyelinating peripheral neuropathy associated with an IgM kappa biclonal gammopathy and reactivity against MAG.[4] It has been found with a higher frequency in patients with motor neuron disease, multiple sclerosis, or nonneurological immune diseases.[10] It has also been detected in 2 cases of CIDP, but with uncertain clinical significance.[9] The other three bands revealing a weak reaction with the patient's serum cannot be associated with any protein known to be important in demyelinating peripheral neuropathy. We do not know if the reactions observed with the patient's serum are due to the same species of antibodies or if different immunoglobulin subclasses are at the origin of the autoimmune reactivity.

We suggest that this child developed a relapsing inflammatory demyelinating polyneuropathy favored by the serum IgA deficiency and by the presence of serum autoantibodies recognizing several PNS proteins.

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SEVERE HYPOKALEMIC MYOPATHY IN GITELMAN'S SYNDROME

Gitelman's syndrome is a disorder with autosomal recessive inheritance that is due to a defective Na-Cl transporter in renal tubules. Spontaneous hypokalemia, hypomagnesemia, and hypocalciuria are its key features.[1] Although

muscle weakness is a common presenting symptom, it is usually mild and well tolerated. Many cases are therefore undiagnosed until a routine plasma electrolyte determination reveals hypokalemia. Here, a Chinese boy who presented at the age of 12 years with a severe myopathy is reported. Features of his muscle biopsy were similar to those observed in familial periodic hypokalemic paralysis. Gitelman's syndrome should be added to the list of differential diagnoses for patients with hypokalemic paralysis.

We encountered a 12-year-old Chinese boy with a 3-week history of proximal muscle weakness and low-grade fever before admission to hospital. An erythematous violaceous skin rash over the face, neck, and front of chest was also noted. The weakness had affected the lower limbs before the upper. There was no previous episode of muscle weakness and he had otherwise been well, without recent diarrhea or urinary symptoms. Plasma potassium level when admitted was 1.6 mmol/L (normal range, 3.5–5.1 mmol/L), and serum creatine kinase was 9700 U/L (normal range, 30–236 U/L). Thyroid function tests were normal. Electromyogram, performed only on the left rectus femoris, showed a myopathic pattern with low-amplitude polyphasic motor unit potentials. Fibrillation potentials were not present. He required large doses of potassium supplements to maintain his potassium level at around 3 mmol/L. In view of the persistent muscle weakness and high creatine kinase level, a muscle biopsy was performed, which showed focal myocyte necrosis and degeneration. Central vacuolation degeneration of myocytes was frequently seen.

The skin rash subsided 2 weeks after admission and full muscle power was only regained after about 1 month, though plasma potassium level was maintained at the lower limit of normal by supplementation. Serum creatine kinase concentration dropped only gradually to 331 U/L over the course of 4 weeks. Further biochemical investigations showed renal wastage of potassium and magnesium, and hypocalciuria. A low serum magnesium concentration (0.45 mmol/L, normal range being 0.67–1.01 mmol/L) was accompanied by an inappropriately high urinary excretion (2 mmol/day). Urinary calcium excretion was low (0.53 mmol/day). A mild metabolic alkalosis (pH 7.49) was related to secondary hyperaldosteronism; supine plasma renin activity was 8.54 ng/mL/h (normal range, 0.12–1.59), and aldosterone level was 761 pmol/L (normal range, 28–445). Oral magnesium chloride was started at a dose of 0.6 mmol/kg/day. Plasma potassium level increased spontaneously to the range of 3.3–3.5 mmol/L without any potassium supplement, and hypomagnesemia was corrected. However, hypercalcemia (2.97 mmol/L) occurred when potassium level was normalized. The magnesium dosage had to be reduced to 0.4 mmol/kg/day before a normal plasma calcium level could be maintained, but plasma potassium concentration then dropped to 3.1 mmol/L. The patient has been followed up for 4 years since presentation and remains well on treatment. Both parents of the patient showed normal plasma electrolyte concentrations.

The most common cause of hypokalemic paralysis occurring in Chinese males is thyrotoxic periodic paralysis.[3] Familial periodic hypokalemic paralysis is more common in the Western population. Other rare causes include primary hyperaldosteronism, diuretics abuse, and diarrhea related to intestinal parasites. Although the familial incidence in Gitelman's syndrome may lead to confusion with familial periodic paralysis or a rare inherited form of thyrotoxic periodic paralysis, the persistence of hypokalemia between attacks of paralysis differentiates it from these two conditions.

Few reports have documented the level of muscle enzymes during paretic episodes. In our case, serum creatine kinase on admission was more than 9000 U/L, approaching the range of rhabdomyolysis. The level was persistent and only returned to a normal level after 1 month, supporting ongoing myocyte injury and enzyme release. The muscle biopsy documented the presence of myocyte necrosis.

The etiology of this syndrome was disclosed recently with identification of mutations in the gene encoding the thiazide-sensitive Na-Cl cotransporter.[2] Mutations have been found among 12 kindreds of Gitelman's syndrome. Inactivating mutations of the gene for this transporter lead to a defective Na-Cl reabsorption in the distal tubule, together with secondary potassium/magnesium wastage. Although a dissociation of the sodium and calcium reabsorption in the distal tubule was observed with thiazide, the exact mechanism leading to hypocalciuria is not fully understood.

Treatment with magnesium supplement alone was successful in this case, though potassium-sparing diuretics, indomethacin, and sodium/potassium supplements have been advocated in the past. However, correction of plasma magnesium may enhance the renal reabsorption of calcium in these patients, who are already hypocalciuric. Therefore, careful monitoring of plasma electrolytes and muscle enzymes, and maintenance of an acceptable plasma potassium level are warranted in the management of patients with Gitelman's syndrome.

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FASCICULAR CONSTRICTION IN THE ANTERIOR INTEROSSEOUS NERVE AND OTHER MOTOR BRANCHES OF THE MEDIAN NERVE

A 35-year-old male office worker developed rubella on April 13, 1997, but improved within a few days. On April 26, the patient experienced the sudden onset of severe pain in the shoulders with no apparent cause, and the next day in both elbows. On April 30, he noticed an inability to flex his left thumb and index finger. The pain diminished after 2 weeks, but the weakness persisted.

When first examined on July 15, there was tenderness over the course of the left median nerve and complete paralysis of the left flexor pollicis longus (FPL), flexor digitorum profundus of the index finger (FDP1), pronator teres (PT), and flexor carpi radialis (FCR). In the right arm, only the FCR was paralyzed. There was no sensory loss. Electromyography (EMG) showed evidence of denervation in the paralyzed muscles and the left pronator quadratus; the muscles around the shoulders were normal. The patient was initially diagnosed as having spontaneous left anterior interosseous nerve (AIN) palsy and right FCR palsy. Motor paralysis did not show any sign of recovery, and on August 13, 1997, surgical exploration of the left median nerve was carried out around the elbow. The median nerve was slightly adherent to surrounding tissues, but no obvious extrinsic compression was observed. The

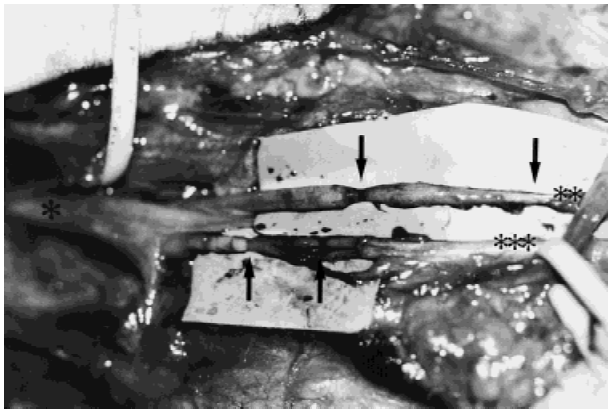

FIGURE 1. Overall view after interfascicular neurolysis. Left side (*) is main trunk of median nerve. Anterior interosseous nerve (AIN, **) and the motor branches of pronator teres and flexor carpi radialis (***) run distally. Each fascicle in the AIN and the branch was constricted at two levels (arrows).

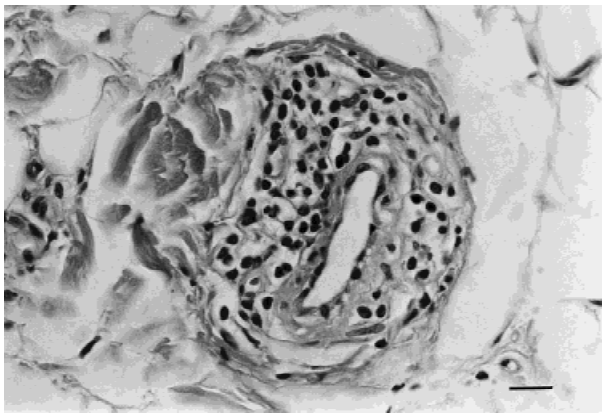

FIGURE 2. Specimen of epineurium of anterior interosseous nerve. Note perivascular lymphoid cell infiltration (scale bar, 20 μm).

AIN was explored in the forearm and traced proximally under microscopy. Two constrictions were found in the fascicles of the AIN in the median nerve at the level of the medial epicondyle and at a region 2 cm more distally. There were also two constrictions in the motor branches of PT and FCR above the medial epicondyle (Fig. 1).

Pathological examination of the epineurium of the AIN showed mild perivascular lymphoid cell infiltration, indicating a slight chronic inflammation (Fig. 2). Six months later, the patient regained the ability to flex his thumb and index finger voluntarily and now has almost fully recovered.

Nagano[4] divided spontaneous AIN palsy into two groups. Group I consists of an isolated AIN palsy, and fascicular constrictions have been described in several reports of such cases.[2,5] Group II is characterized by a combined palsy of PT, FCR, or palmaris longus with AIN palsy but without sensory disturbance. Our case falls within group II, but its pathology was the same as that of group I. We believe that this case satisfies the clinical criteria of neuralgic amyotrophy[1,6] but with a pattern of peripheral nerve lesions that is now well described.[1,3] The cause of these lesions has not yet been established. The patient also showed right FCR paralysis, presumably also as a result of a constrictive lesion of the nerve to this muscle. The pathology involved chronic inflammation of uncertain etiology.[5] Whether the inflammatory response led to scarring, fibrosis, and eventually the constrictive lesions that we found is also unknown.

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