EUR MED PHYS 2000;36:55-60

Electrophysiological evaluation of the peripheral and central pathways in patients with achondroplasia before and during a lower-limb lengthening procedure

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In this paper we review the spectrum of spinal and peripheral nerve involvement secondary to achondroplasia. Alongside conventional and computerised imaging techniques, electrophysiological investigation may represent a useful, non-invasive approach in this clinical setting. Somatosensory evoked potentials (SEPs) and magnetic stimulation are valuable tools for studying spinal cord function. Neurophysiological abnormalities show a good correlation with the lesion level. Imaging techniques indicate that multiple malformation can affect the patient at the same time and SEPs help to determine the main site of involvement. Interestingly, these techniques are more sensitive than clinical evaluation in documenting neurological impairment in patients with achondroplasia prior to the manifestation of unmistakable signs. Callotasi has became a widely used and accepted procedure for limb lengthening. Extensive lengthening can be safely performed in patients with achondroplasia once neurological impairment has been ruled out. In our experience, the presence of electrophysiological abnormalities calls for a comprehensive surgical re-evaluation of the traditional procedure, and sometimes exclusion of patients. Peripheral nerve involvement may occur during limb lengthening, and continuous nerve monitoring provides useful insights into the pathophysiology of nerve damage.

Key words: **Achondroplasia - Electromyography - Somatosensory evoked potentials - Magnetic stimulation - Limb lengthening.**

Submitted for publication January 17, 2000.
Accepted April 12, 2000.

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Neurological involvement in achondroplasia

Achondroplasia is an autosomal-dominant skeletal dysplasia. The clinical features include dwarfism with disproportionate shortening of the proximal limbs (rhizomelia), shallow rib cage, large head with depressed nasal bridge, and characteristic radiographic bony aspects.[1] The genetic defect in enchondral bone formation is associated with neurological complications related in part to spinal canal stenosis and to a small foramen magnum, producing compression of both neural and vascular structures.[2]

The clinical manifestations may be divided into three general categories: 1) macrocephaly and hydrocephalus, 2) cervicomedullary compression and 3) compressive spinal cord and nerve root syndrome. The neurological signs and symptoms encompass a broad spectrum, ranging from mild nerve root irritation to complete paraplegia/quadriplegia. Rarely, devastating neurological dysfunction may occur early in the first few years of life and surgical intervention has to be performed safely.[3] Our experience, as well as that of other clinics, indicates that many achondroplastic individuals are spared most or all of these complications and that those who are affected usually develop signs and symptoms slowly.

Since neurological examination is neither completely specific nor completely sensitive for cervico-medullary compression, i.e. neurological signs, such as upper motor neurone findings have been subtle or absent in many documented cases of cord compression in infancy and childhood,[4 5] these young patients require comprehensive, detailed evaluation with both imaging techniques (CT and MRI scan investigation of the spine) and functional assessment of the neural pathways by electrophysiology (somatosensory evoked potentials and magnetic stimulation of the brain and spinal cord).

Achondroplastic people complain by no means rarely of chronic intermittent low back pain and lower-limb claudicatio; these symptoms may be related to the existence of lumbar spinal stenosis and/or spinal dysraphism. Electromyography and nerve conduction studies (particularly F-wave analysis) have to be performed in order to evaluate the proximal nerve segments.

Neurological deficits secondary to spinal stenosis represent a distinct threat to achondroplastic individuals. The majority of spinal stenoses occur in adult achondroplastic dwarfs in their fourth and fifth decades. Children and young adults, however, appear to account for a higher percentage of symptomatic patients coming to operation than previously suspected. In the same age range, patients are also evaluated with a view to treatment by lengthening of the lower limbs. Our major challenge is to identify correctly the existence of a nervous dysfunction and the level and the extent of the damage through physical and neurological examination along with a detailed electrophysiological investigation: early recognition is of obvious importance and will alert the surgeon to the potential hazards and side effects of bone distraction on the neuromuscular structures.

Lengthening of the lower limbs is a widely used method of correcting bone deformations and a valuable treatment in patients with short stature of varying aetiologies.[6] Extensive lengthening may be accompanied by functional impairment: stretch or compressive injuries to either nerves or muscles have been considered factors of decisive importance.[7 8] Accurately identifying these complications in actual clinical practice may be difficult, but considering them may be the first step towards defining a rational plan of treatment during rehabilitation procedures. We used electrophysiological techniques (nerve conduction study, needle electromyography, F-wave analysis) to monitor the various postoperative phases, investigating the muscles and nerves in close contact with the lengthened bone segments.

Electrophysiological investigation

Somatosensory evoked potentials (SEPs)

Electrical or mechanical stimuli applied at any level can elicit SEPs. Conventionally, an electric shock applied to the usual stimulation sites (mixed nerves of the upper and lower limbs) predominantly activates the large-diameter, fast-conducting group Ia muscle and group II cutaneous afferent fibres.[9] Potentials spreading from the more distal part of the peripheral nervous system reach the plexus and root structures, making it easy to assess the nerve along its entire length. Once the ascending volley enters the spinal cord, a post-synaptic potential can be immediately recorded reflecting the activity of the segmental dorsal grey matter, while, simultaneously, a centripetal travelling wave is mediated almost exclusively by dorsal column tracts. Using a preferential reference montage, a junctional potential generated by propagating volleys arriving at the medial lemniscus at the level of the foramen magnum can be detected.[10] Finally, the activity of the corresponding somatosensory cortex is normally evoked by the sensory stimulus and may be related to different components distributed over the scalp leads. The whole pathway is illustrated in Figure 1, showing a normal tracing in a healthy achondroplastic subject.

SEPs are an important non-invasive means of evaluating patients with achondroplasia and are particularly valuable for documenting neurological impairment before significant and perhaps irreversible clinical damage develops.[3 11] SEP abnormalities show a good correlation with the level of the lesion: imaging techniques indicate that multiple malformations can affect the patient at the same time and SEPs represent an aid in determining the main site of involvement.[12]

The median nerve SEPs may be suitable for studying the bulbo-spinal sensory structures: a prolonged N13-N20 central conduction time is generally found to be associated with a narrowed spinal canal and/or small foramen magnum; the isolated absence of the spinal N13 is invariably related to the presence of dorsal grey matter dysfunction (syringomyelia); when the latter abnormality is accompanied by desynchron-

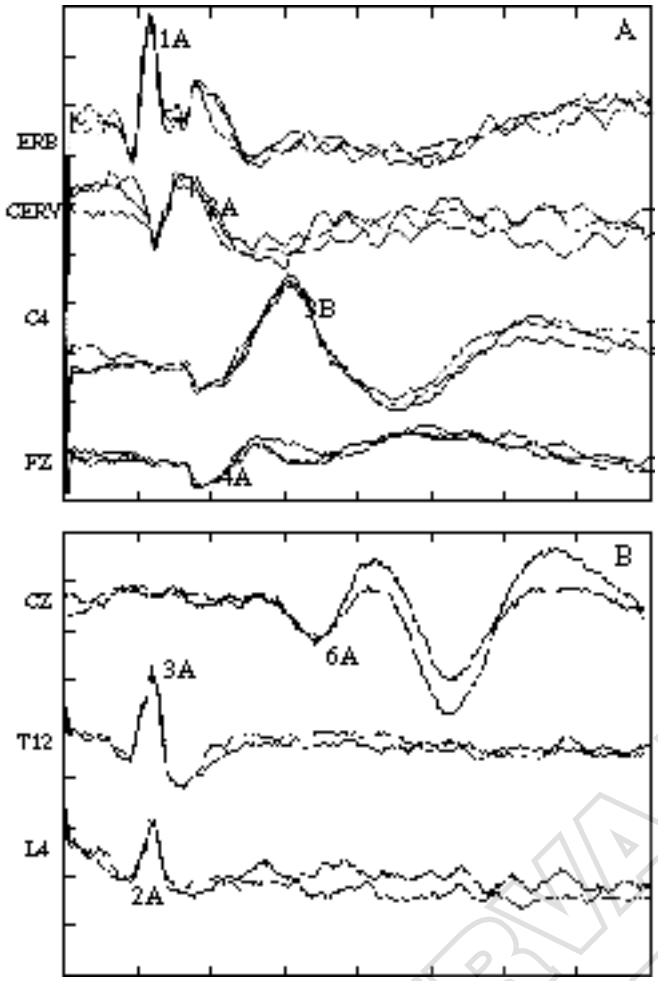

Fig. 1.—Somatosensory evoked potentials (SEPs) in a normal achondroplastic. Upper traces: median nerve SEPs. 1A: N9 ERB point 2A: N13 cervical potential 4A: P14 cervico-medullary junctional potential 3B: N20 cortical potential. CAL: 5 msec/div 2.5 uV/div negative up. Lower traces: posterior tibial nerve SEPs. 2A: P15 lumbar plexus potential 3A: N22 lumbosacral spinal potential 6A: P37 cortical potential. CAL: 10 msec/div 2.5 uV/div negative up. Individual potentials are named using the corresponding label of the adult subject with normal stature(ex: N9 is a negativity occurring with a mean of 9 msec).

ization of the cortical response (N20), the damage is more extensive and posterior tibial nerve SEPs are also abnormal; sensory-motor defects are always evident (ataxic paraparesi).

Lower-limb SEPs are even more sensitive than upper-limb SEPs in revealing spinal cord dysfunction due to spinal stenosis: the delay in central conduction time is the earliest electrophysiological abnormality and can be found in asymptomatic patients.

Magnetic stimulation

This revolutionary technique, introduced a few years ago[13] in the clinical field, uses the short-lasting and strong magnetic field provoked by current discharge within a coil by a bank of capacitors. With the coil in direct contact with the subject's head or spine, such induced electric currents cross the extraneural layers (skin, bone, meninges) with minimal or no activation of pain receptors, resulting in a well-tolerated procedure and making it possible to conduct enough studies in children.[14] The application of the stimulus to the nervous structures is capable of eliciting an electromyographic response called the motor evoked potential (MEP). The responses show variable latencies, depending on the recording site: about 20 msec and 30-40 msec from the brain motor areas to the hand or foot-leg muscles, respectively. These times are related to the activation of oligosynaptic, fast-propagating corticospinal tracts.[15] Magnetic stimulation of the posterior neck or dorsal spine activates spinal roots at the level of the intravertrebral foramen: peripheral conduction time can be obtained by calculating the latency of the MEP which is related to the muscle recording site (usually the thenar eminence and tibial anterior muscle from upper and lower limbs, respectively). The difference between the latency of the response to stimulation of the cortex and spine can be considered as being close to the central conduction time.

Central conduction time abnormalities are frequently found in achondroplastic patients with spinal stenosis and cervico-medullary lesions. A delay in central conduction or the absence of brain MEPs from both the upper and lower limb recordings are usually indicative of involvement of the bulbo-spinal junction and/or upper cervical spine. If such abnormal findings are shown exclusively by the lower-limb MEPs, they can be regarded as indicating low cervical and/or dorsal cord damage. From a pathophysiological point of view, these abnormalities suggest a dysfunction of the spinal motor pathways (pyramidal tracts); they invariably occur when the neurological examination reveals spasticity or a Babinski sign, but can reveal the presence of motor disturbances before their unmistakable clinical appearance.

Lumbar spinal stenosis can affect MEPs, above all by producing a prolonged peripheral conduction time, although F waves and SEPs are more reliable indicators of such levels of nervous entrapment (see below).

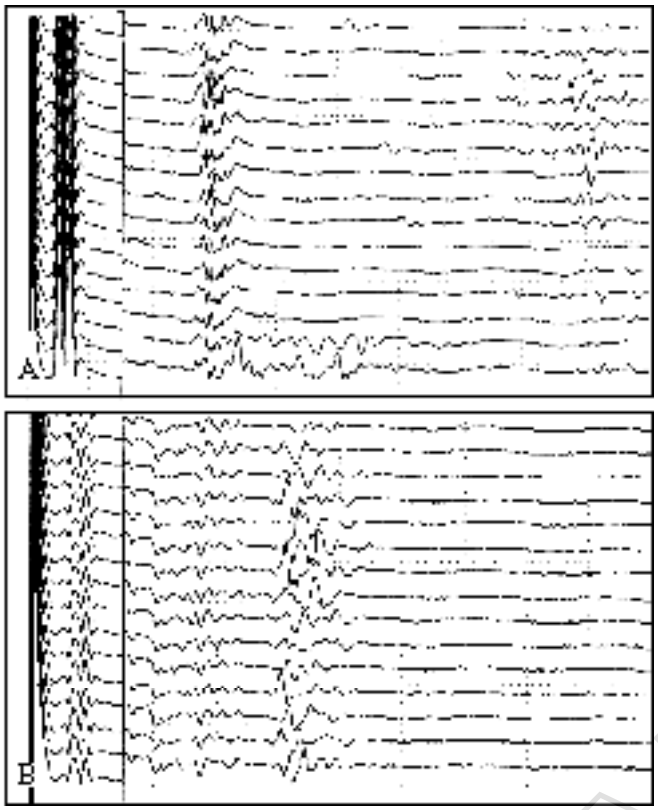

Fig. 2.—F-wave recording. A) M response (direct motor potential) and F wave (late motor potential) in an asymptomatic acondroplastic subject (122 cm high). Several traces are superimposed and rectified: the mean minimum latency is automatically calculated (26.0 msec) at the onset of the F wave. A silent period occurs between M response and F-wave. B) Recording in an achondroplastic patient (120 cm high) complaining of spinal claudication due to lumbar stenosis. The F-wave latency is consistently prolonged (38.6 msec) and pathological late responses (LR) appear between M response and F-wave, both documenting lumbo-sacral root entrapment. CAL: 10 msec/div, 0.250 mV/div; 15 consecutive traces are obtained by stimulation (1 per second) of the posterior tibial nerve at the ankle.

Motor nerve conduction and F-wave evaluation

Conventional nerve conduction studies are a very simple and reliable means of assessing peripheral nerve function.[16] However, they seldom contribute to the investigation of more proximal lesions. In contrast, measurement of the F wave helps in assessing motor conduction along the most proximal segment, because it results from the backfiring of activated motor neurones in the anterior horn of the spinal cord.[17] The latency of the F wave is much longer than the latency of the M response and reflects an impulse travelling from the site of stimulation to the spinal cord and then returning to the distal muscle.[18] A number of reports have suggested clinical value in assessing patients with root injuries and lumbar stenosis.[19-21] The effect of limb length is obviously very important in determining the standardisation of the F-wave latency in control groups: achondroplastic patients should therefore be compared to themselves for statistical analysis.[22]

We have found that an unequivocal delay in F-wave latency in conjunction with normal motor conduction distally is often related to lumbar entrapment of the cauda equina: this finding is particularly characteristic of patients complaining of neurogenic claudicatio (very frequent in achondroplastics) but without detectable signs at clinical examination (Fig. 2).

Peripheral nerve involvement may occur during limb lengthening, and continuous nerve monitoring provides useful information for our understanding of the pathophysiology of nerve damage.[23] Patients undergoing callotasi using the conventional approach introduced by our orthopaedic surgeons [6] were asymptomatic from the neurological point of view (both clinical and electrophysiological). In these patients, the only neurological complication was some degree of peroneal nerve palsy always occurring following tibial callotasi: the extent of the lengthening was not the main factor involved and distraction of the proximal bone segment (femur) is not a predisposing condition, while an important risk factor for nerve damage may be surgical stress.[22]

Conclusions

In this paper, we have illustrated the electrophysiological techniques currently used to study the function of the peripheral and central nervous pathways in greater detail. These techniques are more sensitive than clinical evaluation in documenting neurological impairment in patients with achondroplasia before the appearance of unmistakable signs. This fact is of particular importance in the early years when life-threatening conditions may be encountered. Initially, they may provide the clinician with the first diagnostic information.

Callotasi has become a widely used and accepted procedure for limb lengthening. Extensive lengthening can be safely performed in patients with achondroplasia once neurological impairment has been

ruled out. In our experience, the presence of electrophysiological abnormalities calls for a comprehensive surgical re-evaluation of the traditional procedure, and sometimes exclusion of the patient.

During callotasi, surgical stress and bone distraction may be associated with peroneal nerve palsy and nerve stretching: electrophysiological monitoring of the different phases of the lengthening helps to delineate the pathophysiology of the nerve damage, a factor conditioning the rehabilitative treatment.

Riassunto

Valutazioni elettrofisiologiche nel paziente acondroplasico prima e durante l'allungamento degli arti inferiori

L'Acondroplasia è caratterizzata da un difetto dell'ossificazione encondrale per una alterazione della cartilagine di coniugazione: è nota l'anomalia genetica (braccio corto cromosoma 4) che viene trasmessa con modalità di tipo autosomico dominante. Tale difetto è responsabile dello scarso accrescimento di numerose ossa piatte del massiccio cranio – facciale, della colonna vertebrale, del bacino e delle ossa lunghe degli arti (nanismo rizomelico).

Le problematiche auxologiche sono spesso associate alle manifestazioni cliniche di origine neurologica. Queste ultime possono essere considerate conseguenti a stenosi del forame magno e/o del canale midollare e avvengono con segni di: 1) idrocefalo e macrocefalia, 2) compressione bulbo – spinale e 3) sindromi da compressione mielo – radicolare. La gravità e la prognosi sono in genere correlate all'età di insorgenza. L'idrocefalo, presente in circa il 60% dei casi, è sintomatico in meno del 5%; in questo caso l'ipertensione endocranica richiede un intervento di derivazione ventricolo – peritoneale.

La patologia della giunzione bulbo – spinale coinvolge il 20 – 47% dei casi ed è dovuta a malformazione della cerniera atlo – occipitale (ristrettezza del forame magno, malformazione di Arnold – Chiari). Il rischio di morte improvvisa da arresto cardio – respiratorio avviene nel 7,5% nel corso del primo anno e nel 2.5% tra il I e IV anno.

Gli effetti clinici della stenosi del canale (cervicale e/o lombare) sono chiaramente più tardivi e contribuiscono ad una variabile invalidità. Nell'evoluzione naturale, la sindrome da stenosi lombare (claudicatio, low - back pain, disturbi sfinterici) compare nel 20 - 30% dei pazienti, sia nella tarda infanzia che nell'età adulta (III - IV decade) e nel 10% circa viene eseguita una laminectomia decompressiva.

I segni neurologici dei giovani acondroplasici, in cui può essere posta indicazione all'intervento di allungamento già nei primi anni di vita, possono essere, quindi, espressione di disfunzioni congenite stabilizzate (segni di 1° motoneurone) oppure di sindromi lentamente evolutive (compressioni mielo-radicolari).

Poiché l'esame neurologico non è sufficientemente sensibile, visto che i segni di primo motoneurone sono difficili da riconoscere anche in casi documentati di compressione cervico-midollare, sottoponiamo i pazienti a procedure diagnostiche e di follow-up molto dettagliate, sia di tipo radiologico (Risonanza Magnetica Nucleare) che di tipo elettrofisiologico per lo studio del sistema nervoso centrale (Potenziali Evocati Acustici, Somatosensitivi e Motori) e periferico (Elettromiografia e Velocità di Conduzione).

Dopo alcuni tentativi con somministrazione di GH, l'unica possibilità di intervento per migliorare la statura finale del soggetto affetto da Acondroplasia risulta ancora oggi l'allungamento chirurgico degli arti inferiori, che consente, tramite l'acquisizione di parecchi centimetri, notevoli miglioramenti della qualità della vita di relazione.

La Callotasi con metodo crociato è la strategia proposta dalla scuola di Verona: viene consigliata nella prima parte della seconda decade di vita per la collaborazione che deve essere offerta dal paziente, soprattutto nel programma di recupero funzionale.

L'allungamento degli arti può essere accompagnato da qualche problema intercorrente legato al danno del nervo periferico, che viene monitorato strettamente con metodiche elettrofisiologiche: si può assistere, così, ad un disturbo del peroneo comune con deficit della flessione dorsale del piede che compare molto precocemente rispetto alla chirurgia della tibia ed è quindi molto probabilmente legato all'atto operatorio (ematoma, ischemia locale): nelle fasi successive il recupero clinico avviene anche a dispetto della distensione delle parti molli conseguente all'allungamento osseo. Questa evoluzione si verifica regolarmente qualora il paziente sia indenne da qualsiasi precedente disfunzione neurologica: il nostro obiettivo è, quindi, identificare correttamente l'esistenza di segni clinici o strumentali, l'estensione ed il livello di danno neurologico. Le informazioni così ottenute consentono di allertare il Chirurgo sugli effetti secondari della Callotasi e dell'allungamento sulle strutture neuromuscolari.

Il monitoraggio elettrofisiologico precoce (potenziali evocati) è stato eseguito in 13 bambini di età compresa tra 2 mesi e 4 anni, con registrazioni ad intervalli regolari di 4 - 6 mesi. Lo studio della stenosi spinale (potenziali evocati somatosensitivi, stimolazione magnetica transcranica e spinale, elettromiografia) è stato eseguito in 15 pazienti compresi tra 16 e 54 anni. L'effetto dell'allungamento degli arti sulla funzione nervosa periferica (potenziali evocati somatosensitivi e studio della conduzione) è stato condotto su 11 pazienti di età compresa tra 13 e 22 anni.

Parole chiave: Acondroplasia - Arti, allungamento - Elettromiografia - Potenziali evocati somatosensitivi.

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