

## Letters to the Editor

### Ultrasonography of MADSAM neuropathy: Focal nerve enlargements at sites of existing and resolved conduction blocks

I read with great interest the article by Scheidl et al. [1] focused on the ultrasonography findings of the acquired demyelinating sensory and motor neuropathy (MADSAM). The authors depicted for the first time in the literature, that focal nerve enlargements can be detected by ultrasound in MADSAM, at sites of previous conduction blocks, well after complete clinical and electrophysiological resolution. This observation highlights in my opinion two important aspects in the clinical course of the disease. On one side, it shows that ultrasonographic morphological changes may outlast functional recovery in such demyelinating neuropathies. On the other side, this study highlights the fact that although the clinical course of the disease is expected to be predominantly in the upper extremities, morphological changes to the nerves of the lower extremities can be detected by ultrasound prior to clinical and electrophysiological affection.

A similar sonographical observation has been done only in the case of multifocal motor neuropathy (MMN) by Beekman et al. [2]. They reported in a study of 21 patients, that a sonographic enlargement could be found not only in nerve segments without conduction abnormalities indicating demyelination, but also in nerves with normal conduction.

In our neurophysiologic and ultrasound lab we recently started to perform ultrasound in patients affected from immune-mediated neuropathies. Experiencing a case of a MADSAM neuropathy with disease course over 2 years, we detected sonographically a hypertrophy of the median and ulnar nerve in the forearm on both sides, but no pathological findings could be detected in the lower extremities. The site where the hypertrophy was detected in ultrasound correlated with the site of conduction block in the electrophysiological studies.

Considering the study from Scheidl et al. and our findings we would like to draw attention to the usefulness of ultrasonography for detecting and diagnosing segmental lesions of the peripheral nerves in MADSAM and other immune-mediated neuropathies. These findings indicate that the disease process in MADSAM is more widespread than expected on the basis of clinical and electrophysiological abnormalities. In our case though, we could not detect any pathological abnormalities in the lower extremities, so the time course of the disease may play an important

role for the detection of these changes. Unfortunately there are no histologic studies of nerves in MADSAM without electrophysiologic abnormalities that could confirm these ultrasound findings. These ultrasound observations could help though to understand the underlying mechanisms of nerve damage and facilitate the development of more effective treatments.

### References

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### Stem cells in severe infantile spinal muscular atrophy (SMA1)

Dear Sir,

We would like to share our recent experience on the use of intrathecal mesenchymal stem cells in children with type I spinal muscular atrophy (SMA) as we believe it raises several issues of concern.

Human mesenchymal stem cells (hMSCs) are known to secrete a variety of cytokines and growth factors that show both paracrine and autocrine activities for damaged tissues, including nervous cells. The paracrine effects are distinct from the classical model of direct differentiation of stem cells into the tissue to be regenerated, and are supposed to have a possible pivotal role in various forms of nervous cells damage [1].

Their therapeutic role has been recently proposed in some human and animal models of second motoneuron

neurological damage, such as amyotrophic lateral sclerosis and spinal cord injury [2–6] and their use through intrathecal injection has proved to be well tolerated in a number of central nervous system degenerative diseases [7–9]. Other studies have demonstrated a possible positive effect of such therapy in slowing the progression of neuronal damage in animals [10].

The successful application of hMSCs in other disorders had a strong impact in public opinion and an order of the local Court solicited our hospital to use them as compassionate therapy in SMA, as requested by some families. Following the consent of the Local Ethical Committee, we agreed to start a compassionate treatment in a small number of SMA1 patients under the agreement that (a) the clinical and neurophysiological effects of the treatment should be strictly monitored and (b) the Hospital had the right to withdraw treatment in the presence of side effects or if no obvious effect of the treatment could be observed after 6 months. Each family signed a module of informed consent and, intrathecal injection was chosen to deliver the cells, as previously performed in patients with spinal cord injury and amyotrophic lateral sclerosis.

Between December 2010 and December 2011 five type I SMA children (1 m, 4 f, age range: 3–20 months) were enrolled. Mesenchymal stem cells were supplied by the Stem Cell Facility of the San Gerardo Hospital, Monza, Italy. Cells were administered on a monthly basis for 6 months. At each admission, the following evaluations were performed: a general clinical assessment (weight, respiratory function, feeding), assessment of motor function, using the CHOP Intend Scale, a functional scale specifically developed for children with type I SMA [11], and video recording of the assessment and of spontaneous movements. The cerebrospinal fluid collected before each injection was analyzed by measuring the concentration of 48 proteins (Bio-Rad human cytokine and growth factors set 27plex and 21plex).

One of the five patients who entered the study, enrolled at the age of 13 months, died from respiratory failure at the age of 18 months, 1 month after the second injection. The family of another patient asked to stop the treatment after the 5th injection, at 8 months of age, and the child died at the age of 12 months of respiratory failure. The other three patients completed the 6 month treatment course. During this period in all three there was the need to initiate supportive therapy with nutritional and respiratory aids. In all three patients there was a progressive decline of motor function as demonstrated by the reduction of the CHOP Intend scale total score and no clinical evidence of any improvement.

There were no reproducible changes in concentration of the proteins dosed in the cerebrospinal fluids before, during or after treatment.

The Hospital asked an external Scientific Board including experts in stem cells and SMA to review the results of the study. The clinical course of the treated patients showed no improvement and did not differ from the recent

natural history data available in infants with SMA1 [12]. Because of the lack of efficacy, in December 2011 the hospital, in accordance with the local Ethical Committee, decided to stop recruitment.

Our experience raises important issues on the need to have a more rigorous approach to clinical trials. Our results support the need for strong experimental data in disease specific animal models to strengthen the rationale of a study in a specific disorder and anticipate clinical application of therapeutic approaches. Although no serious adverse effects was noted, a more systematic and conventional approach to safety, with dose escalation studies would have further reduced the risk for these patients and could have also provided better information on the dose and the treatment regime.

More generally, our findings highlight the risk that the combination of newspaper ‘hype’ and parental ‘hope’, with the support of courts that are sympathetic to families with children with severe disorders, may produce shortcuts in the design of clinical studies that would need more rigorous preclinical information and more accurate safety and efficacy measures and may actually put patients at risk of potential side effects of therapy.

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