Two Patients with Sporadic Late-Onset Nemaline Myopathy Respond to Stem Cell Therapy

BY PAULA MOYER

ARTICLE IN BRIEF

Two patients with sporadic late-onset nemaline myopathy — one in the Netherlands, the other in France — responded dramatically to a combination of melphalan and autologous stem cell therapy.

Neurologists rarely see patients with sporadic late-onset nemaline myopathy (SLONM), and when they do, the prognosis is grim: patients typically die within five years after its onset, after progressively losing limb-girdle muscle tissue and the ability to get out of bed, dress themselves, and swallow.

DR. OLIVIER BENVENISTE: "Our center has seen exactly six cases during the last 13 years. For the first time, we may be onto something."

Recently, though, investigative teams in the Netherlands and France each treated a patient with SLONM with a combination of melphalan and autologous stem cell therapy. Their reports, published in the Aug. 12 *Neurology,* showed that each patient responded dramatically.

[These cases were not typical nemaline myopathy, however; rather the patients had a monocolonal gammopathy associated with nemaline bodies in muscle.]

At 15-months follow-up, the 38-year-old man from the Netherlands was "able to walk upstairs and run again; speaking and swallowing were normal," said the senior study author Baziel van Engelen, MD, PhD, professor of neurology at the University of Nijmegen in the Netherlands. He had also returned to work.

And in the French case, at 24 months, a 63-year-old woman — who used a wheelchair and needed assistance for all activities of daily living — could walk easily without the help of a cane. In both cases, the post-treatment histology reports showed that the patients' muscle cells were free of nemaline rods.

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Dr. van Engelen told *Neurology Today* in an e-mail: "Treatment by melphalan and stem cell transplant in this patient resulted in considerable clinical improvement, which was supported by histology."

LONG-TERM EFFECTS UNKNOWN

Dr. van Engelen cautioned that because SLONM is very rare, there is no database to determine the long-term effect of melphalan and stem cell transplantation. Therefore, the next step is to increase the awareness of SLONM and to continue to follow the patient that is the basis of this case report, he wrote.

Speaking to the rarity of SLONM, Olivier Benveniste, MD, PhD, the principal investigator of the French case who is a professor of medicine at Groupe Hospitalier Pitié-Salpêtrière in Paris, said in a phone interview: "Our center has seen exactly six cases during the last 13 years. For the first time, we may be onto something."

He agreed with Dr. Van Engelen that the rare nature of SLONM means that the number of patients studied will always be small and that SLONM patients eventually die of their disease within five years. Therefore, it is probably impossible and inadvisable to use the conventional clinical trial approach that is based on patient recruitment and statistical analyses.

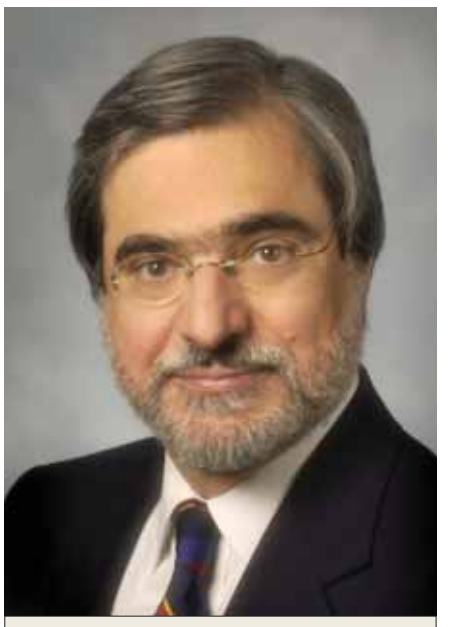
However, he said, the results in these two cases may speak for themselves. "When you see someone who cannot get out of bed, and then can walk quite easily a few months later, you don't need a large cohort of cases," he said. "Other neurologists may want to try this approach. For the first time, there may be a future for these patients."

Eventually SLONM investigators may want to try less aggressive treatments, than inductional graft protocols, he said. The two teams will be collaborating and sharing information on these two patients, Dr. van Engelen wrote.

EXPERTS COMMENT

Two experts found the results very heartening. "Considering the dismal nature of this disease and its relentless course, the clinical response is impressive," wrote Marinos C. Dalakas, MD, and Stephan A. Smith, MD, in an accompanying editorial. Dr. Dalakas, professor of neurology at Thomas Jefferson University in Philadelphia, wrote: "The rationale for using such therapy in SLONM was based on the effectiveness of melphalan and bone marrow transplantation in patients with plasma cell dyscrasia and amyloidosis. … The improvement, independently demonstrated by two different centers, is convincing and one would not expect a controlled trial for such a rare disease."

DR. STEVEN A. GREENBERG: "Although the disease is rare, [the research] is of greater interest because neurologists in the trenches often wonder if there might be some effective treatment for the many other poorly responsive diseases we treat."



DR. MARINOS C. DALAKOS: "Extreme caution should be exercised before using such high-risk therapy," which entails a mortality rate of more than 13 percent.

However, he cautioned that "extreme caution should be exercised before using such high-risk therapy," which entails a mortality rate of more than 13 percent. He cited several questions for ongoing research, including the potential for safer therapies for SLONM and the applicability of the melphalan/stem cell approach for patients with other untreatable muscular diseases in which, like SLONM, monoclonal gammopathies are often present. Examples he cited were inclusion body myositis and amyotrophic lateral sclerosis (ALS).

Commenting on the study, Steven A. Greenberg, MD, assistant professor of neurology at Brigham and Women's Hospital and Harvard Medical School in Boston, said: "Although the disease is rare, [the research] is of greater interest because neurologists in the trenches often wonder if there might be some effective treatment for the many other poorly responsive diseases we treat."

"Perhaps the treatment used here for this disease might work for others," he added. "In this regard, attention is largely focused on other diseases that are believed mediated by the immune system, since the disease here (SLONM) is believed to be mediated by the immune system and the treatment used suppresses the immune system." However, he cautioned that it is not yet known whether the treatment would work for other au-

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Epilepsy, Other Neurological Disorders Linked to Survival of Cerebral Malaria

BY ED SUSMAN

CHICAGO—More than 30 percent of children who survive bouts with cerebral malaria suffer from neurologic pathologies such as epilepsy and attention deficit hyperactivity disorder (ADHD), according to a study conducted in the African nation of Malawi.

Doctors who studied 93 children who survived cerebral malaria — a disease that can be fatal about 20 percent of the time — said they were significantly more likely to be diagnosed with epilepsy, unprovoked seizures, developmental abnormalities, and ADHD when compared to similar children who were hospitalized for non-cerebral malaria conditions.

"In our very short follow-up of between six and 21 months, we have already had about 6 percent of our kids develop clear epilepsy; another 10 percent have had their first unprovoked seizure," said Gretchen Birbeck, MD, MPH, associate professor of neurology and epidemiology at Michigan State University in East Lans-

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toimmune neurological diseases.

Dr. Greenberg was also concerned about the perils of using melphalan and stem cell therapy. One strategy may be to offer patients with SLONM the high-dose melphalan plus stem cell therapy used in these studies or "perhaps a potentially equally effective but less toxic treatment." An example he gave was such as standard-dose melphalan plus high-dose dexamethasone, which proved similarly effective in patients with immunoglobulin-light-chain (AL) amyloidosis in other research published in 2007 in *The New England Journal of Medicine*.

AL amyloidosis, the most common form of systemic amyloidosis in the US, is characterized by multiple organ involvement and a median survival of one year with no treatment. "The less toxic treatment might be considered for a subset of other patients with autoimmune neurological diseases," Dr. Greenberg

REFERENCES:

- Voermans NC, Minnema M, van Engelen BG, et al. Sporadic late-onset nemaline myopathy effectively treated by melphalan and stem cell transplant. *Neurology* 2008;71:532-534.
- Benveniste O, Laforet P, Eymard B, et al. Stem cell transplantation in a patient with late-onset nemaline myopathy and gammopathy. *Neurology* 2008;71:531-532.
- Dalakas MC, Smith SA. A "nema" of hope in the treatment of late-onset nemaline myopathy. *Neurology* 2008;71:472-473.474.
- Jaccard A, Moreau P, Leblond V, et al. High-dose melphalan plus dexamethasone for AL amyloidosis. *NEJM* 2007;357:1083-1093.