Longitudinal Patterns of Thalidomide Neuropathy in Children and Adolescents

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Objective To characterize the longitudinal clinical and electrophysiological patterns of thalidomide neuropathy in children and adolescents.

Study design Retrospective analysis of clinical records at a tertiary care children's hospital, including serial electrophysiological studies.

Results Sixteen patients aged 6-24 years received thalidomide to treat Crohn's disease from 2002 to 2012. Nine subjects had electrophysiological evidence of sensorimotor axonal polyneuropathy, 8 of whom had sensory and/or motor symptoms. The patients with polyneuropathy received thalidomide for 5 weeks to 52 months, with cumulative doses ranging from 1.4 to 207.7 g. All subjects with cumulative doses greater than 60 g developed polyneuropathy, and 4 of the 5 subjects who received thalidomide for more than 20 months developed polyneuropathy. The 7 subjects who had normal neurophysiological studies received therapy for 1 week to 25 months, with cumulative doses ranging from 0.7 to 47 g. In contrast to some previous reports, several patients had sensorimotor polyneuropathies, rather than pure sensory neuropathies. In patients with neuropathy who received therapy for more than 24 months and had 3 or more electromyography studies, the severity of the neuropathy plateaued.

Conclusions Factors in addition to the total dose may contribute to the risk profile for thalidomide neuropathy, including pharmacogenetic susceptibilities. The severity of the neuropathy does not worsen relentlessly. Children, adolescents, and young adults receiving thalidomide should undergo regular neurophysiological studies to monitor for neuropathy. *(J Pediatr 2016;178:227-32).*

Thalidomide ([RS]-2-[2,6-dioxopiperidin-3-yl]-1H-isoindole-1,3[2H]-dione) is a glutamic acid derivative with anti-inflammatory, immunomodulatory, sedative, and antiemetic properties.[1-3] It gained popularity in the late 1950s, notably among pregnant women, because of its antiemetic effects.

In the early 1960s, however, thalidomide was withdrawn from pharmaceutical markets worldwide after recognition of its teratogenic effects.[4-6] In recent years, thalidomide's potent anti-inflammatory and immunomodulatory effects have led to a renaissance in its status as an acceptable medication for a variety of dermatologic, immunologic, and neoplastic disorders, such as erythema nodosum leprosum[7-9] and multiple myeloma.[10] In children, it has become an important component of the armamentarium for Crohn's disease,[11-14] Behçet syndrome,[15] plexiform neurofibromas,[16] juvenile idiopathic arthritis,[17] and mucocutaneous graft-vs-host disease.[7,8,14-19] Careful precautions are now taken to avoid its use in pregnant women, and thus the most significant side effect that commonly is encountered is peripheral polyneuropathy, which can limit the clinical use of thalidomide in both adults[6,20,21] and children.[22,23] Although there is longstanding awareness of thalidomide-associated polyneuropathy,[24] this side effect remains poorly characterized, and current literature regarding the incidence, risk factors, and management of polyneuropathy has been contradictory.[22,25,26]

The aims of the current study are to examine the incidence of polyneuropathy in children and adolescents receiving thalidomide for Crohn's disease (9 of 16), to describe associated clinical and neurophysiological features in those patients with polyneuropathy, and to determine the cumulative dose associated with this toxicity. In addition, we report our experience with the management of thalidomide neurotoxicity and longitudinal changes in electrophysiological measures for those patients who had multiple assessments.

Methods

The Committee on Clinical Investigation (institutional review board) of Boston Children's Hospital approved this retrospective study of 17 children, adolescents,

CMAP	Compound motor action potential
EMG	Electromyography
SNAP	Sensory nerve action potential

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The authors declare no conflicts of interest.

http://dx.doi.org10.1016/j.jpeds.2016.07.040

and young adults who received thalidomide for Crohn's disease at the hospital between 2002 and 2012. The medical records of these subjects were reviewed, including demographic information, clinical notes, and electromyography (EMG) reports. One patient who had only a baseline EMG during the study period was excluded, leaving 16 for full analysis. Particular attention was given to the presence of neurologic symptoms and cumulative thalidomide doses. The decision to initiate maintenance thalidomide therapy for the management of Crohn's disease was made by the primary treating gastroenterologist. Evaluation of any adverse events, with special attention to any signs and symptoms of involvement of the peripheral nervous system, was conducted at every outpatient visit. The standard recommendation was to perform neurophysiological studies before the onset of treatment and every 6 months during treatment; however, adherence to this schedule varied as the result of various clinical circumstances. When available, baseline neurophysiological results were used to look for interval changes during subsequent studies.

Neurophysiological studies were performed in the EMG Laboratory of Boston Children's Hospital, primarily with a CareFusion Synergy N5EP system (Natus Medical Incorporated, Pleasanton, California). Standard procedure during the period of investigation was to measure skin temperatures before the start of the study and warm extremities as needed to maintain temperatures at 32°C or greater in the upper extremities and 30°C or greater in the lower extremities. Compound motor action potentials (CMAPs) and antidromic sensory nerve action potentials (SNAPs) were measured with standard techniques on selected nerves. Concentric needle EMG was performed on selected muscles in the upper and/or lower limbs as indicated clinically.

For the purposes of this study, the presence of polyneuropathy was defined exclusively by electrophysiological criteria. Axonal polyneuropathy was characterized by reduced sensory and/or motor nerve amplitudes on nerve conduction studies, with standard reference ranges.[27,28] Findings suggesting ongoing denervation and/or chronic reinnervation on needle EMG also were noted in support of the presence of axonal polyneuropathy.

Demyelinating polyneuropathy was characterized by slowing of nerve conduction velocities. Clinical symptoms suggestive of the presence of polyneuropathy included distal paresthesias, pain, numbness, and/or weakness.

Children diagnosed with clinical or electrophysiological polyneuropathy often, but not always, had a reduction in the thalidomide dose based on feedback from the electrophysiological studies, with ongoing clinical and electrophysiological monitoring of their peripheral nerve function recommended.

The cumulative dose of thalidomide in grams received by each patient was calculated from the medical records. These cumulative doses along with duration of therapy were compared between patients who developed neuropathy vs those who did not by use of a 2-tailed *t* test (SigmaPlot version 13.0; Systat Software, Inc, San Jose, California).

Selected SNAP and CMAP amplitudes that were measured longitudinally were tracked over time. Sensory nerves that typically were included were the median, ulnar, sural, and superficial peroneal. Motor nerves that typically were included were the median, ulnar, peroneal, and tibial. The exact selection varied by subject, depending on which nerves underwent repeat measurement across multiple studies, enabling quantitative analysis of changes over time. The total SNAP and CMAP amplitudes were compared with duration of therapy and cumulative thalidomide dose, to determine the electrophysiological course of neuropathy.

Results

Sixteen children with Crohn's disease who were receiving ongoing thalidomide therapy were included in the study. There were 12 male and 4 female patients, with an age range of 6-24 years. The mean duration of therapy was 14.9 months, and the mean cumulative dose of thalidomide was 42.9 g. A total of 33 neurophysiological studies were analyzed, with 10 patients having 2 or more studies and 5 patients having 3 or more studies.

Nine of the 16 patients developed electrophysiological evidence for an axonal polyneuropathy; none of these patients were found to have a demyelinating polyneuropathy. Their ages ranged from 9 to 24 years at baseline evaluation, and there was no clear relationship between the age of initiation of thalidomide therapy and the development of polyneuropathy. These patients received thalidomide therapy for a mean duration of 20.8 months (range 5 weeks to 52 months), with a daily dose of 50-150 mg and a mean cumulative dose of 63.5 g (range 1.4-207.7 g). The abnormalities were more pronounced in the lower extremities, suggesting the presence of a length-dependent polyneuropathy.

Six of the 9 patients with electrophysiological polyneuropathy developed sensory symptoms, 2 patients had both sensory symptoms and mild weakness, and 1 patient did not have clinical symptoms of polyneuropathy. Among the patients with electrophysiological polyneuropathy, 2 had improvement of their electrophysiological measurements and symptoms after dose reduction and 3 had no improvement in their polyneuropathy despite dose reduction. The remaining 4 patients had a reduction of their thalidomide dose, but at the time of the study, had not had a follow-up nerve conduction and EMG study. With a reduction in dose, although there was no electrophysiological improvement in 3 patients, the sensory and motor nerve action potential amplitudes remained stable with no perceptible worsening of the polyneuropathy. No patients discontinued thalidomide treatment.

The 7 children who had normal neurophysiological studies received therapy for a mean duration of 7.4 months (range 1 week to 25 months), with a daily dose ranging from 25 to 100 mg and a mean cumulative dose of 16.5 g (range 0.7-47 g). Their ages ranged from 6 to 23 years at baseline evaluation. Three of these 7 children reported mild sensory symptoms, but there was no electrophysiological evidence for a peripheral neuropathy, and thus those patients were determined not to have a large fiber neuropathy.

The mean interval from onset of therapy to onset of peripheral neuropathy was 10.2 months. The age ranges of the