Peripheral Nerve Toxic Effects of Nitrofurantoin

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Objective: To investigate the role of skin biopsy in nitrofurantoin peripheral neuropathy.

Design: We describe the clinical features and skin biopsies of 2 cases of non–length-dependent small-fiber neuropathy/ganglionopathy attributable to nitrofurantoin.

Setting: Clinical evaluation and skin biopsies were performed at a tertiary teaching hospital in Baltimore, Maryland.

Patients: A 59-year-old woman with disabling generalized dysesthesia and a 53-year-old woman with progressive burning pain in the perineum and extremities.

Main Outcome Measures: Slow or incomplete recovery and possibly irreversible damage.

Results: The neuropathy was neither dose dependent nor associated with impaired renal function. Results from nerve conduction studies were normal. Skin biopsies revealed distinctive morphologic changes with clustered terminal nerve swellings without evidence of nerve fiber degeneration.

Conclusions: These distinct morphologic changes associated with nitrofurantoin have not been previously reported to our knowledge. Skin biopsy appears to be helpful in confirming the diagnosis in these patients.

Nitrofurantoin is an antibiotic used mainly in the treatment of urinary tract infections. Nitrofurantoin neuropathy, predominantly a length-dependent sensorimotor neuropathy, has been described. We describe 2 patients with relatively short exposure to nitrofurantoin who developed non–length-dependent neuropathic pain. While clinical examination and conventional nerve conduction study findings were unremarkable, the results from skin biopsies were abnormal with distinctive morphologic changes. The unrelenting course of dysesthesias despite discontinuation of nitrofurantoin in the 2 patients may suggest irreversible damage.

NITROFURANTOIN IS AN ANTIBIOTIC USED MAINLY IN THE TREATMENT OF URINARY TRACT INFECTIONS. NITROFURANTOIN NEUROPATHY, PREDOMINANTLY A LENGTH-DEPENDENT SENSORIMOTOR NEUROPATHY, HAS BEEN DESCRIBED. WE DESCRIBE 2 PATIENTS WITH RELATIVELY SHORT EXPOSURE TO NITROFURANTOIN WHO DEVELOPED NON–LENGTH-DEPENDENT NEUROPATHIC PAIN. WHILE CLINICAL EXAMINATION AND CONVENTIONAL NERVE CONDUCTION STUDY FINDINGS WERE UNREMARKABLE, THE RESULTS FROM SKIN BIOPSIES WERE ABNORMAL WITH DISTINCTIVE MORPHOLOGIC CHANGES. THE UNRELENTING COURSE OF DYSESTHESIAS DESPITE DISCONTINUATION OF NITROFURANTOIN IN THE 2 PATIENTS MAY SUGGEST IRREVERSIBLE DAMAGE.

REPORT OF CASES

CASE 1

A 59-year-old woman had a 2-year history of generalized patchy dysesthesias. Her medical history was significant only for interstitial cystitis. Two years prior, she had been treated with prophylactic nitrofurantoin, 100 mg daily, for urinary retention following the repair of a bladder prolapse. Four weeks into the therapy, she reported generalized dysesthesias with prickly heat and sunburnlike sensations, which were pronounced in the thighs, shoulders, and neck. She developed generalized livedo reticularis and photosensitivity across her face and extremities. Her symptoms persisted despite discontinuation of nitrofurantoin. The results from extensive investigations including autoimmune and connective tissue serology were unremarkable. A trial of high dose prednisolone acetate, 60 mg/d relieved her symptoms, but they recurred on prednisolone tapering. Treatment with antihistamine and leukotriene blockers had no effect on her symptoms. She was fatigued and lost 6.80 kg.

Neurologic examination revealed preserved muscle strength and tendon reflexes in all extremities. Sensory examination was intact to vibration, proprioception, light touch, and pin prick. Her gait was normal and her Romberg Test was negative. Results from a nerve conduction study (NCS) were unremarkable. Her skin biopsy showed normal intraepidermal nerve fiber density (INFD), with pronounced morphologic changes of clustered swellings of terminal nerve fibers.
Her neuropathic symptoms were managed with gabapentin and duloxetine hydrochloride, providing partial relief. At 3 years, she continued to be symptomatic.

**CASE 2**

A 53-year-old woman had a 6-month history of dysesthesias. Her medical history was significant for psoriasis treated with metotrexate sodium. She was prescribed nitrofurantoin for 1 week for a urinary tract infection, after which she developed burning pelvic pain. Assuming recurrent urinary tract infections, she failed to respond to multiple trials of oral antibiotics. Laparoscopic examination found no cause for her pelvic pain. Her symptoms worsened to involve her hands, feet, shoulders, thighs, and perineum and were described as intense burning. She had flulike symptoms with malaise, headache, and arthralgia, and she lost 11.33 kg.

Physical examination revealed no lateralizing signs or motor deficits. She had intact sensation to light touch, temperature, vibration, and proprioception. Her Romberg Test was negative.

Results from extensive investigations including folate, vitamin B₆, and vitamin B₁₂ levels; methylmalonic acid levels; celiac serology; parvovirus B19 IgM; autoimmune serology (including Sjögren antibodies); Lyme serology; parvovirus B19; Lyme serology; pernicious anemia screen; heavy metal screen; thyroid function test, and serum protein electrophoresis were all unremarkable. Cerebrospinal fluid examination revealed a glucose level of 55 mg/dL (to convert to millimoles per liter, multiply by 0.0555), protein level of 67 mg/dL, and white blood cell count of 1/µL (to convert to ×10⁶ per liter, multiply by 0.001) with negative flow cytometry. Nerve conduction studies and electromyography results were normal, with a right sural amplitude of 40.8 µV and velocity of 40 m/s. A skin biopsy revealed INFD that was within the normal limits. There were morphologic abnormalities, with clustered terminal nerve fiber swellings (Figure). She began treatment with duloxetine hydrochloride and transdermal fentanyl, with significant improvement of her symptoms allowing for resumption of work and exercise. Findings from repeated skin biopsy performed 6 months later were essentially unchanged, with persistent axonal swellings and normal INFD (Figure).

**SKIN BIOPSY**

Punch biopsies were performed with a 3-mm disposable circular punch (Acupunch; Acuderm) after the injection of lidocaine hydrochloride, 2%, under an aseptic technique. Biopsy specimens were obtained from the lateral aspect of the following sites: the upper thigh (10 cm above the greater trochanter), the distal thigh (10 cm above the patella), and at the ankle (10 cm above the lateral malleolus). Specimens were fixed in Zamboni solution, and free-floating 50-µm sections were immunostained with the panaxonal marker protein gene product 9.5 (ubiquitin hydrolase; ABD Serotec). For each biopsy, at least 3 sections were read. The epidermal fibers were identified, counted, and documented as the number of intraepidermal nerve fibers per millimeter of epidermis. The morphology of nerve fibers was observed. Technical details have previously been described.

**COMMENT**

Nitrofurantoin was first introduced in 1952. It is a synthetic antimicrobial derived from furan by the addition of a nitro group and a side chain containing hydantoin. Its antibacterial spectrum is broad and is particularly effective against *Escherichia coli* and *Klebsiella* and *Enterobacter* species, hence its use for the treatment of urinary tract infections. Nitrofurantoin is excreted and concentrated in the urine. In the presence of impaired renal function, the urine levels fall below the therapeutic range while the serum levels increase into the toxic range. Thus, its efficacy is limited in the setting of renal impairment, with an associated greater risk of toxic effects and adverse reactions.

Nitrofurantoin is an overall relatively safe drug. Primary adverse effects are predominantly gastrointestinal tract symptoms with nausea, emesis, and anorexia. Peripheral neuropathy is a less-recognized adverse reaction. The first case of peripheral neuropathy attributable to nitrofurantoin was reported by de Fine Olivarius in 1956. Since then, many more cases and reviews have been published, although these were mainly reported in the 1960s through 1980s.
Typically, nitrofurantoin neuropathy manifests as length-dependent sensorimotor polyneuropathy. The glove and stocking pattern of sensory symptoms were accompanied by varying degrees of motor weakness in the same pattern of distribution, with muscle atrophy of the intrinsic muscles in severe cases. Only 2 cases with perineum disturbance have been reported. Most patients had moderate to severe abnormal sensory and motor conduction on NCS and axonal degeneration on sural nerve biopsy.

In contrast, our patients had non–length-dependent small-fiber neuropathy/ganglionopathy. The first patient presented with generalized body dysesthesias, while the second patient had predominantly perineum symptoms with subsequent involvement of the extremities. Their NCS and electromyography results were unremarkable, thus excluding large-fiber polyneuropathy. Skin biopsies revealed normal INFD but abnormal morphology, with clustered swelling of the nerve fibers. Both patients were female and in their 50s. The duration of the exposure and cumulative doses were relatively short: 4 weeks of a prophylactic dose in the first patient and only 1 week of a therapeutic dose in the second patient. Both patients had normal renal function. Despite discontinuation of nitrofurantoin, the symptoms progressed unabated. The first patient had persistent symptoms, albeit with some improvement, 3 years following discontinuation of nitrofurantoin.

Symmetric, non–length-dependent neuropathic pain involving proximal regions of the limbs, face, and trunk, either sparing the acral extremities or with simultaneous involvement of both proximal and distal extremities, suggests a selective disorder of the dorsal ganglia cells subserving small nerve fibers. The commonly implicated causes include glucose intolerance, Sjögren syndrome, paraproteinemia, celiac disease, hepatitis C, and paraneoplastic syndrome and are idiopathic in most cases. Our cases suggest that neurotoxic neuropathy must also be considered in the differential diagnoses.

Skin biopsy is a useful investigation to confirm the diagnosis of small-fiber neuropathy. Length-dependent small-fiber neuropathy demonstrates the typical proximal-distal gradient of INFD density, confirming the length-dependent loss of cutaneous innervation. Conversely, ganglionopathy or non–length-dependent small-fiber neuropathy in patients with hyperesthesias reveals a distinct pattern of epidermal denervation, with either normal INFDs on all sites or loss of INFD proximally but preservation distally.

The morphologic changes of clustering of swelling of nerve fibers in the papillary dermis are most unusual. This morphologic feature is not unique to nitrofurantoin and has also been observed in ganglionopathy and small-fiber neuropathy secondary to Sjögren syndrome.

The mechanisms for the prediction for the nerve fibers, in particular small-caliber fibers, in the papillary dermis are unknown. Nitrofurantoin interferes with pyruvate oxidation by competing with thiamine pyrophosphate. However, neurotoxic neuropathies from other causes (eg, vitamin B₆ excess) are not associated with such nerve fiber changes on skin biopsy.

Although axonal swellings have been found to predict the degeneration of epidermal nerve fiber in painful neuropathies in some patients, the repeated skin biopsy 6 months later in our second patient revealed no reduction of fiber density. This suggests that the axonal swellings associated with nitrofurantoin may not be a harbinger to subsequent epidermal nerve fiber degeneration.

Various drugs have been implicated in neurotoxic neuropathy. More than 50 compounds including antimicrobials, antineoplastics, antiretrovirals, and cardiovascular, hypnotic, and psychotropic drugs have been implicated. Clinicians have to be vigilant to the possible neurotoxic effect of any medication, especially in elderly patients or those with impaired renal function. Careful neurologic examination and NCS complemented by either sural nerve biopsy or skin biopsy may help to establish the diagnosis. Referral for skin biopsy in the clinical setting of small-fiber neuropathy with normal NCS findings is helpful to confirm the diagnosis and potentially sheds light on the mechanism of injury. Early recognition of the cause and removal of the implicating drug will aid recovery and may reverse the injury. Corticosteroid may have a role, although the withdrawal was associated with the rebound of patients’ symptoms. Nitrofurantoin may precipitate an autoimmune ganglionitis that is partially responsive to corticosteroid, as in the process implicated in nitrofurantoin-induced autoimmune hepatitis.

In conclusion, nitrofurantoin neuropathy may present with a wide spectrum of manifestations, more commonly large-fiber sensorimotor neuropathy and small-fiber neuropathy. Non–length-dependent neuropathy/ganglionopathy is rarely described in neurotoxic neuropathy. Nitrofurantoin neuropathy has a characteristic morphology as demonstrated in these cases. Skin biopsy helps to confirm the diagnosis and plays an important role in the management of these patients.


