Acrylamide neuropathy
Michael T Pulley MD PhD (Dr. Pulley of the University of Florida, Jacksonville, received honorariums from Alexion, CSL Behring, and Grifols for consulting work.)
Alan R Berger MD (Dr. Berger of the University of Florida, Jacksonville, and Director of the Shands Jacksonville Neuroscience Institute has no relevant financial relationships to disclose.)
Louis H Weimer MD, editor. (Dr. Weimer of Columbia University has received consulting fees from Roche.)
Originally released December 3, 1999; last updated April 12, 2017; expires April 12, 2020

Introduction

Overview
The authors discuss the clinical manifestations of acrylamide neuropathy. This toxic neuropathy has served as a model for studying the effects of toxins on the nervous system. Recently, new information has emerged regarding the potential mechanism of the neuropathy. This may completely change the approach to research of toxic neuropathies.

Key points
• Acrylamide causes a central-peripheral distal axonopathy.
• The neuropathy in animals is predictable and has been used as a model for other forms of central peripheral distal axonopathy.
• As with many toxic neuropathies, the manifestations are dose dependent, and the prognosis is dependent on the degree of central axonal degeneration.

Historical note and terminology
The neurotoxic effects of acrylamide have been known for over 50 years (Kuperman 1958; Fujita et al 1960). Acrylamide is used in grouting agents for soil and sealing applications (Kjuus et al 2004), and polyacrylamide is used in flocculating wastewater treatment plants (Feldman 1999). The monomer is the toxic form, whereas the polymer is innocuous. However, the polymer may be contaminated by up to 2% monomer and can, thus, be a source of toxicity. Acrylamide is readily absorbed by inhalation, ingestion, or dermal contact. Acrylamide neuropathy has been a popular experimental animal model for studying the processes of axonal transport (Miller and Spencer 1984; Gold et al 1985), dying-back neuropathy (Schaumburg et al 1974), and axonal swelling. More recently, studies have raised doubts about the basic underlying mechanism of acrylamide neuropathy (LoPachin and Gavin 2015).

Clinical manifestations

Presentation and course
The manifestations of acrylamide toxicity depend on the degree and duration of exposure. The usual route of exposure is through the skin; therefore, a contact dermatitis is usually present prior to the clinical symptoms of neuropathy. In the setting of acute exposure, malaise, dizziness, anorexia, and headache are often present. With high-level acute exposure, the neurologic picture includes encephalopathy with seizures and truncal ataxia followed by peripheral neuropathy (Berger and Schaumburg 1996). Early behavioral changes may be more or less apparent to the patient than others. With more chronic, low-level exposure, the dermatitis persists, but the CNS effects are not as prominent.

The neuropathy resulting from acrylamide is an example of a central-peripheral distal axonopathy. This describes a process whereby the distal portion of the longest peripheral axons are affected first, but with continued exposure, the distal segments of corticospinal, spinocerebellar, and dorsal column axons become subsequently involved (Spencer and Schaumburg 1976). Early clinical manifestations include toe numbness and widespread hyporeflexia. Large fiber sensory dysfunction with loss of vibration and proprioception is common, whereas pain and paresthesias are rare (Schaumburg et al 1974). Acute, high-level exposure often results in widespread autonomic dysfunction such as impairment of reflex, changes in heart rate and blood pressure, vasomotor changes in fingers and toes, and excessive sweating. Overt autonomic dysfunction is less common in chronic exposure and may be limited to excessive sweating.
of the hands and feet. Although sensory complaints dominate, motor and cerebellar deficits may be evident on physical examination. Cranial nerve function is unaffected.

**Prognosis and complications**

Removal from exposure usually results in recovery if the neuropathy is mild. Some residual loss of vibratory sensation may be apparent. However, in the case of severe neuropathy, spasticity, and ataxia, more profound sensory dysfunction and memory problems may remain. Central nervous system dysfunction, such as spasticity and upper motor neuron weakness, may be obscured initially by the peripheral nerve dysfunction. As nerve recovery ensues, clinical dysfunction may remain due to unresolved central nervous system dysfunction. Coasting, the worsening of symptoms after termination of exposure, may occur (Berger et al 1992).

**Biological basis**

**Etiology and pathogenesis**

Acrylamide is absorbed by inhalation, dermal contact, or ingestion. Most occupational intoxication occurs through the dermal route. Both the parent compound and its metabolite, glycaminide, are neurotoxic (Abou-Donia et al 1993). Acrylamide appears to selectively accumulate in the distal portions of peripheral nerves (Ando and Hashimoto 1972). A decrease in the activity of glutathione-S-transferase activity may be related to the onset of neuropathy (Dixit et al 1981). Acrylamide exposure may have effects on genes involved in apoptosis, at least in rats (Li et al 2006). Acrylamide alters the profile of cytoskeletal proteins in the sciatic nerves of rats and this may be related to the mechanism of neuropathy (Yu et al 2006).

**Cell biology.** Acrylamide appears to interfere with axonal transport (Miller and Spencer 1984; Gold et al 1985), resulting in an accumulation of neurofilaments and axonal swelling (Schaumburg et al 1989). The swelling is most prominent in the paranodal region, possibly due to the constriction of the axon at that point (Spencer and Schaumburg 1977). The reduction in fast axonal transport is not dependent on neurofilaments, as transgenic mice without axonal neurofilaments also have reduction in fast axonal transport when exposed to acrylamide (Stone et al 2000). In addition to the effects on axonal transport, high-level acute exposure has been shown in animals to cause chromatolysis in the dorsal root ganglion cells (Tandrup 2002). Morphologic studies using silver stain have shown that the dose and acuity of exposure determine whether the damage is primarily at the nerve terminal or there is involvement of axons (Lehning et al 2003). The same group of investigators has subsequently extended this observation (LoPachin et al 2003). They found that with 2 separate dosing regimens, nerve terminal damage was the initial manifestation of acrylamide toxicity. These researchers now question the significance of axonal swelling and feel it is a secondary event and not the primary mechanism of neuronal dysfunction. Studies of acrylamide neuropathy in rats have shown a correlation between neurophysiologic changes and altered levels of glutathione (reduced) and malondialdehyde (increased), suggesting oxidative stress may play a role in the mechanism of disease (Zhu et al 2008). Finally, although small fiber dysfunction is not a primary manifestation clinically, skin biopsy studies in mice show early changes in intraepidermal nerve fibers (Ko et al 2002).

**Epidemiology**

Acrylamide neuropathy is almost exclusively an occupational exposure problem.

**Prevention**

Education of the potentially toxic effects of acrylamide is the first step toward preventing disease related to exposure. As dermal absorption is a potential source of exposure, protective clothing and gloves should be worn. Good personal hygiene should be stressed (eg, washing hands prior to eating). Adequate ventilation can help prevent respiratory exposure, and respirators should be used in areas with high levels in the air. In animal models, the immunosuppressant FK506 (tacrolimus) has been demonstrated to protect against acrylamide neuropathy (Gold et al 2004). This protective effect may be mediated by upregulation of heat shock protein.

**Differential diagnosis**

Any other etiology of a slowly progressive, symmetric, distal axonopathy should be considered in the differential diagnosis. The combination of a sensory greater than motor neuropathy and spasticity raises the possibility of B12
deficiency (subacute combined degeneration). The clinical findings of contact dermatitis, excessive sweating of the extremities, and a sensory greater than motor neuropathy, in the proper clinical setting, should prompt inquiry regarding acrylamide exposure.

**Diagnostic workup**

Neurophysiologic testing reveals reduced amplitude sensory responses with preservation of motor amplitude and conduction velocity (Fullerton 1969). These findings are characteristic of a distal axonopathy. In some instances the electrophysiologic abnormalities may precede the development of symptoms. The sural nerve biopsy correlates with the physiologic and clinical manifestations showing reduced numbers of large diameter, thickly myelinated fibers (Cavanaugh 1964). Studies have demonstrated that both acrylamide and glycinamide can be detected in minute quantities in rat plasma, and that this may be applicable to humans (Barber et al 2001).

**Management**

Preventing further exposure to acrylamide is the primary treatment modality. Acute ingestion should prompt gastric lavage to reduce levels of intoxication. Liver and renal failure may necessitate blood transfusions or hemodialysis. In cases where there is significant residual sensory loss or weakness, the patient may benefit from rehabilitation including physical and occupational therapy to improve function. Spasticity can be managed using baclofen or tizanidine.

**Special considerations**

**Pregnancy**

A study of dietary history found that pregnant mothers consuming foods with higher acrylamide content had lower birthweight infants (Duarte-Salles et al 2013).

**References cited**


Fullerton PM. Electrophysiologic and histologic observations on the peripheral nerves in acrylamide poisoning in man. J Neurol Neurosurg Psychiatry 1969;32:186-92. PMID 4307538


Li SX, Cui N, Zhang CL, et al. Effect of subchronic exposure to acrylamide induced on the expression of bcl-2, bax and caspase-3 in the rat nervous system. Toxicology 2006;217:46-53. PMID 16242231


**References especially recommended by the author or editor for general reading.**

**ICD and OMIM codes**

**ICD codes**

ICD-9:
Polyneuropathy (peripheral) caused by accidental poisoning by corrosives and caustics not elsewhere classified: 357.7, E864.2

ICD-10:
Polyneuropathy due to other toxic agents: G62.2

**Profile**

**Age range of presentation**

19-44 years  
45-64 years

**Sex preponderance**

male=female

**Family history**

none

**Heredity**

none

**Population groups selectively affected**

none selectively affected

**Occupation groups selectively affected**

manufacturing plant workers

**Differential diagnosis list**

distal axonopathy

**Associated disorders**

Dermatitis  
Encephalopathy

**Other topics to consider**

Chronic autonomic neuropathies  
Introduction to and clinical evaluation of peripheral neuropathies  
Introduction to toxic peripheral neuropathies

Copyright © 2001-2018 MedLink Corporation. All rights reserved.