Neurotoxicology: a clinical systems-based review

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ABSTRACT

Neurological disease caused by toxins is widespread but under-recognised. Despite increasing public interest and a growing number of novel potential neurotoxins, diagnosis of neurotoxic disease is often delayed or missed, resulting in poorer patient outcomes. This article discusses neurotoxic syndromes using a systems-based approach, focusing on environmental and occupational agents. We do not discuss recreational drugs, pharmaceutical agents or developmental neurotoxins in detail. We aim to provide neurologists with a working understanding of the scenarios in which a clinical presentation may be due to a neurotoxin and how to approach confirmation of the diagnosis.

INTRODUCTION

A neurotoxin is any naturally occurring or synthetic agent that adversely affects the structure or function of the nervous system.[1] The high metabolic rate, size and postmitotic state of neurones and other associated cells make the nervous system especially vulnerable to damage by toxins. The blood–brain barrier provides only incomplete protection because it can be degraded, is permeable to lipophilic toxins and is absent at several sites including the pituitary gland, area postrema and choroid plexus endothelium. Poisoning of the nervous system can occur in a broad range of scenarios, and neurotoxins can cause a wide variety of different neurological syndromes. Neurotoxins are often a late consideration, and it is likely that many neurotoxic conditions remain undiagnosed. It is, therefore, important for neurologists to be able to recognise potential neurotoxic diseases.

There are several questions to address in sequence with the patient experiencing possible neurotoxicity, discussed in turn below.

1. Could this presenting syndrome be caused by a neurotoxin?
2. Has this patient been exposed to a known neurotoxin?
3. Could this neurotoxin be the direct cause of the patient's presentation?
4. How can the diagnosis be confirmed?
5. What are the management options?

First, 'Could this presenting syndrome be caused by a neurotoxin?'. The answer here is usually yes because neurotoxins cause such a wide range of different neurological syndromes. This range reflects both the vast number and variety of neurotoxins and also the different vulnerabilities of each component of the nervous system.

The second question then is 'Has this patient been exposed to a known neurotoxin?'. Answering this question requires a detailed and thorough exposure history (see box 1), coupled with a knowledge of contexts in which neurotoxic exposures might occur. These contexts can broadly be grouped into environmental, occupational, deliberate (ie, intentional poisonings), pharmaceutical and recreational. These categorisations, of which only the first three are the focus of this review, are fluid and dynamic. Many occupations that were previously associated with significant neurotoxin exposure no longer exist, or legislation has rendered them safer. Conversely, new groups of people are coming into contact with potential neurotoxins, through the development of new industrial processes, through environmental phenomena such as global warming and even through shifting geopolitical landscapes. Even when there has been a confirmed exposure, this is not inevitably responsible for a patient's presentation. The relative rarity of neurotoxicity, coupled with the frequency of other, non-neurotoxic neurological diseases, means that exposure may be incidental and of no clinical significance. This phenomenon has been termed 'pseudoneurotoxicity'.[2]

Box 1 Important questions to ask in the history

- What is the patient's occupation?
- What are their hobbies and recreational activities?
- Do their symptoms improve when they are away from certain environments, for example, at the weekend?
- Have others around the patient been affected by similar symptoms?
- Take a thorough drug history including any over-the-counter medications, herbal preparations or Ayurvedic medications.
- Take a thorough travel history.

Thus, having established exposure to a particular neurotoxin, it is necessary to answer a third question: 'Could this neurotoxin be the direct cause of the patient's presentation?'. To answer this question requires an understanding of the typical presentation associated with the neurotoxin. This question is particularly challenging to answer because many neurotoxins have different effects in different contexts. Chronic exposure to a low dose of neurotoxin may produce a neurological syndrome different from exposure to an acute, larger dose. Host factors are also important, particularly renal and hepatic function and age. A further challenge is that a temporal relationship between exposure and presentation, though helpful, may not always be present. For example, effects may be delayed if the toxin is sequestered and released later by some separate process. This is the case for bone-sequestered lead released during breastfeeding.[3] Some neurotoxic effects continue to progress after exposure has ceased, a phenomenon known as coasting.

If the clinical syndrome could potentially be explained by the neurotoxic exposure, then the next question is, 'How can the diagnosis be confirmed?'. Diagnostic investigation of neurotoxicity can be challenging. Table 1 (and relevant sections of this paper) summarise specific tests for individual neurotoxins. General considerations include which tissue to sample, whether exposure is acute or chronic, and the degree to which a normal or abnormal level (concentration) is clinically useful. For neurotoxins that are rapidly cleared, blood levels fall rapidly and urine testing may be more appropriate (either 24 hours or random sampling). Arsenic, inorganic mercury and thallium are all better detected by urinalysis. The commonly performed 'heavy metals screen' on blood may therefore be falsely reassuring if negative. Several neurotoxins are sequestered and standard tests may not reflect total body load, particularly in chronic toxicity. 'Normal' value ranges in neurotoxicology are often of only limited use, and false positives and negatives are common, for several reasons. For some syndromes, levels do not correlate well with clinical severity. For others, even levels above the standard normal range (usually 2 SD from the mean) may not be clinically relevant. Dietary practices, particularly fish consumption, can increase the measured levels of neurotoxins such as mercury and arsenic in the absence of clinical effects, compounding the issue of pseudoneurotoxicity. The problem of normal values is further complicated by the fact that we do not fully understand whether mildly elevated neurotoxin levels can result in subtle clinical deficits. Together, these factors represent further challenges in interpreting undifferentiated panels of toxin tests, especially when the investigations are not guided by typical clinical syndromes.

Several imaging patterns are relatively suggestive of neurotoxicity. Bilateral signal change on MRI is particularly typical. Specific imaging patterns are discussed in the relevant sections and are the subject of dedicated reviews.[4] Aside from their location, imaging changes generally reflect either cytotoxic or vasogenic oedema. In both, T2 signal is high. However, cytotoxic oedema occurs with cell lysis and diffusion is restricted (high signal on diffusion-weighted imaging, DWI). In contrast, vasogenic oedema results from toxic insults to the blood–brain barrier and is associated with minimal or no diffusion restriction on DWI. Imaging changes may be delayed and may correlate poorly with the extent of clinical deficit.

Other investigations can help in diagnosing neurotoxicity, in particular nerve conduction studies (NCSs) and electromyography (EMG), although these often lack specificity (apart from with organophosphates).

Once a neurotoxic diagnosis has been confirmed, the final question is how best to manage the condition. We discuss management only briefly as, beyond removing the offending agent, this requires specialist advice and should be guided by the local poisons information service (see box 2). One particular issue, especially relevant to neurologists, is the long-term behavioural effects associated with several neurotoxins, either after a single, large exposure or from chronic, low-level exposure. These effects can be challenging to diagnose and manage. Neurobehavioural changes may be subtle: patients variably report depression, anxiety or forgetfulness and symptoms are often overlooked.[1] There are available psychiatric and psychological assessments for cases of suspected neurotoxicity.[5]

To help neurologists answer the questions above, we have structured this article around clinical syndromes and discuss the most common causative neurotoxins. We present the clinical features that can help suggest a toxic cause and those that point to one toxin over another. Table 1 summarises this information. In practice, many neurotoxins cause more than one distinct clinical syndrome so the focus has been on the most predominant or common syndrome associated with a particular toxin. Sometimes, the constellation can be diagnostically useful, for example, the cerebellar syndrome and peripheral neuropathy of organic mercury toxicity. Given the huge number of potential neurotoxins, we do not attempt to discuss them all.

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Table 1 Clinical syndromes with common causative agents, associated clinical features, typical sources of exposure and preferred diagnostic tests

Syndrome	Toxin	Associated features	Typical sources of exposure	Diagnostic tests
Grey matter encephalopathy	Carbon monoxide	Headache and dizziness Delayed neuropsychiatric syndrome Parkinsonism	Faulty heating appliances	Arterial or venous carboxyhaemoglobin for acute/recent exposure Raised lactate Bilateral globus pallidi necrosis on MRI
	Lead	Gastrointestinal symptoms Peripheral neuropathy	Lead mining, smelting, manufacture or recycling of batteries, old water pipes	Whole blood lead level for acute/recent exposure Microcytic anaemia and basophilic stippling in chronic exposure
	Inorganic mercury	Fine tremor with superimposed myoclonus. Neuropsychiatric disturbance Gingivitis Nephrotic syndrome	Inhalation of vapour from spilled mercury, for example in industrial or laboratory settings Traditional herbal remedies Skin-whitening preparations	Urinary mercury level
Leukoencephalopathy	Toluene and other organic solvents	Solvent-smelling breath Cerebellar and brainstem involvement Alleviation of symptoms at the weekend	Multiple industrial contexts including use of paints and glues	MRI showing diffuse periventricular and subcortical hyperintense T2/FLAIR signal
Cerebellar syndrome	Organic mercury	Perioral and acral numbness Visual field constriction, cortical blindness	Consumption of fish, especially, for example, shark and swordfish	Whole blood mercury level
Parkinsonism	Manganese	Parkinsonism with minimal or no tremor 'Cock-walk' gait Preceding psychiatric changes	Metalwork and welding	Whole blood manganese level for acute/recent exposure T1 hyperintensity in globus pallidi on MRI with normal T2 signal
	Carbon monoxide	See above Prominent axial rigidity	See above	See above
	Methanol	Encephalopathy Optic atrophy	Solvents, antifreeze and the improper preparation of ethanol	Whole blood in fluoride oxalate collection tube Raised anion gap metabolic acidosis MRI showing bilateral haemorrhagic putaminal necrosis
Peripheral neuropathy	Arsenic	Acute: GI prodrome followed by encephalopathy and multisystem involvement (renal failure, anaemia), garlic breath, metallic taste Chronic: Brown palmar desquamation/hyperkeratosis and Mees lines	Contaminated groundwater, mining, smelting and traditional Chinese and Indian medicines Deliberate use	Urinary arsenic level (total or inorganic)
	Lead	Motor predominant neuropathy with early wrist drop Constipation/GI symptoms	See above	Whole blood lead level NCSs showing motor predominant axonal polyneuropathy, preferentially affecting radial nerve. EMG showing evidence of denervation.
	Thallium	Painful sensory neuropathy Alopecia, reversal of sleep-wake cycle and mild gastrointestinal disturbance	Pesticides or contaminated food Deliberate use	Urinary thallium level
	Acrylamide	Sensory predominant neuropathy Dermatitis, erythema and excessive sweating of hands	Manufacture of adhesives, grout and water cleaning agents.	Acrylamide haemoglobin adducts in blood NCS showing axonopathy
	Ciguatoxin	Acral and perioral parasthesia Paradoxical temperature reversal, cold allodynia, itching	Ingestion of reef fish or their predators (eg, red snapper, grouper and barracuda)	No specific diagnostic test but NCS may show generalised slowing and prolonged F-waves
	Organophosphates	Lower limb predominant sensorimotor neuropathy delayed 1–3 weeks following exposure May follow cholinergic symptoms	Agricultural pesticides	Plasma cholinesterase activity NCS showing axonopathy
Myopathy and muscular weakness	Botulinum toxin	Progressive paralysis with dilated pupils	Therapeutic procedures, improperly cooked foods, contaminated honey	Botulinum toxin in blood or faeces Wound swabs to identify C.Botulinum EMG shows reduced compound muscle action potentials
	Snake venoms	Puncture wounds on skin Coagulopathy	Exotic snakes	None in routine use
Autonomic dysfunction	Organophosphates	Parasympathetic overactivity with weakness and muscle fasciculations. Possible associated delayed proximal and respiratory muscle weakness and/or delayed neuropathy	Agricultural pesticides, nerve agent exposure	Plasma cholinesterase activity Characteristic EMG findings
	Trichloroethylene (TCE)	Autonomic neuropathy. Bilateral trigeminal sensory neuropathy and other cranial neuropathies. Increased risk of Parkinson's Disease	Degreasing agents, solvents, paints and glue Improper disposal of industrial waste	No routinely used test but TCE and its metabolites can be detected in urine up to 2 weeks postexposure

EMG, electromyography; FLAIR, fluid-attenuated inversion recovery; GI, gastrointestinal; NCS, nerve conduction studies .

Box 2 Contact details for further advice

- National Poisons Information Service (NPIS). The NPIS is usually the first port of call for healthcare professionals managing any poisonings in the UK. Their website, www.toxbase.org, contains information on a wide range of agents, or they can be called 24/7 on +44 344 892 0111.
- In cases of suspected chemical incidents, assistance should be obtained rapidly from the national Emergency Coordinated Scientific Advice system, by calling +44 300 3033 493. The clinical management of individual patients is supported by NPIS.
- For cases of suspected botulism, contact the UK Health Security Agency's Gastrointestinal Bacteria Reference Unit, on +44 20 8327 7887 or gbru@ukhsa.gov.uk.

Instead, we have focused on those environmental and occupational toxins most likely to be encountered in clinical practice. We also discuss neurotoxins used as weapons or used with the intention of causing harm, which we have termed 'deliberate' neurotoxins. We do not discuss the neurotoxic effects of pharmaceutical agents, recreational drugs or developmentally neurotoxic agents, which all deserve their own separate reviews.

CLINICAL SYNDROMES

Grey matter encephalopathy

Encephalopathy is a very common manifestation of neurotoxicity and is often accompanied by other, more specific, clinical features, such as movement disorders or peripheral neuropathy. Neurotoxins can predominantly affect grey matter structures (grey matter encephalopathy), white matter (leukoencephalopathy) or both (mixed encephalopathy). As the most metabolically active tissue, grey matter is usually the target of toxins that interfere with neuronal energy utilisation. Damage to the energy-intensive cortex is characteristic, and basal ganglia structures may also be involved. The most common toxic causes of grey matter encephalopathy are carbon monoxide (CO), lead and inorganic or elemental mercury.

Carbon monoxide

CO is produced by the incomplete combustion of carbon fuels, as may occur in faulty wood, gas or coal burners. CO interrupts oxygen delivery to neurones through formation of carboxyhaemoglobin and also acts directly on the electron transport chain. At low levels of exposure, the only symptoms may be headache, dizziness, nausea, abdominal pain and subtle cognitive deficits. With such non-specific symptoms, the diagnosis of chronic CO toxicity is frequently missed. Exposure to higher concentrations of CO can result in damage to basal ganglia structures and parkinsonism (discussed below). A hallmark of CO toxicity is the delayed encephalopathy with prominent neuropsychiatric symptoms, which occurs in up to 30% of patients following apparent recovery.[6] The delay ranges from days to several months.

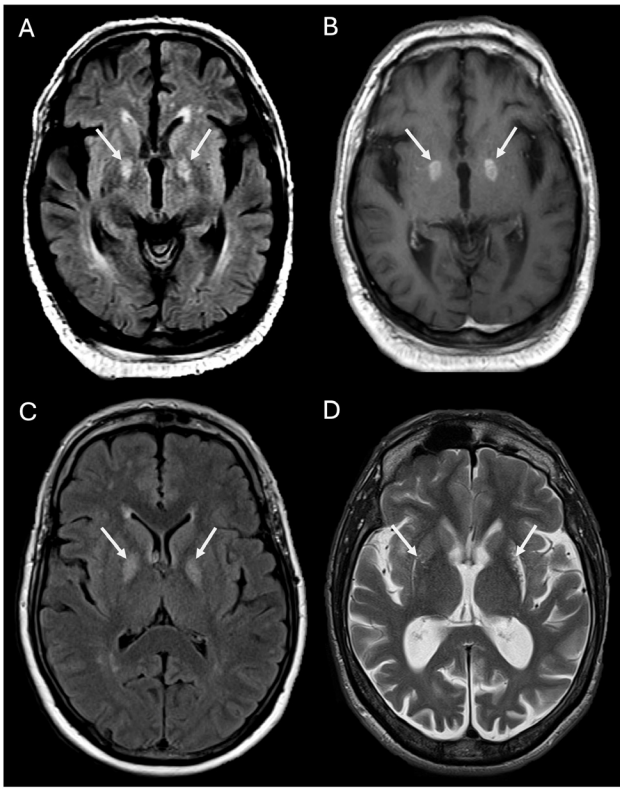

Figure 1 MR scans of brain. Axial FLAIR sequence (A) and postcontrast T1-weighted (B) in a patient in their 50s with suspected carbon monoxide poisoning shows symmetrical high T2w/FLAIR signal in both globus pallidi with corresponding high T1w signal and enhancement suggesting necrosis (arrows). Axial FLAIR sequence (C) in a different patient in their 60s with suspected carbon monoxide poisoning showing similar bilateral abnormal pallidal signal (arrows). Axial T2w sequence in a patient in their 30s (D) 20 years after carbon monoxide poisoning shows a less common imaging finding of secondary mature damage in both putamina (arrows), plus symmetrical parieto-occipital predominant cerebral volume loss. FLAIR, fluid-attenuated inversion recovery.

Blood gas analysis can show an elevated concentration of carboxyhaemoglobin but this correlates only loosely with symptoms and reflects only acute exposure. Serum lactate is often elevated. At higher levels, CO causes characteristic MR brain scan changes of bilateral necrosis of the globus pallidi (figure 1). Less commonly, the MR scan may show putaminal involvement and cerebral volume loss (figure 1D) or white matter changes.

An extremely important component of acute management is to give oxygen. More chronic symptoms require supportive management but it is important to prevent further exposure. Environments in which exposure may have occurred should be assessed and monitored.

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Lead

Lead miners and smelters, and those who work in the manufacture or recycling of batteries are most at risk of acute lead exposure. Acute exposure to high concentrations of lead is now rare in developed countries. However, chronic, low-level exposure causes significant morbidity worldwide. Exposure to paints or lead water pipes in older houses is a significant source of chronic exposure. Lead is especially toxic to children and it is increasingly recognised that there is no safe minimum lead concentration for children.[7] In adults, 95% of whole-body lead is sequestered in bones. In children, this is only about 70%, which partly explains their lower tolerance. Lead may be released from bone in the context of breast feeding or osteoporosis so the symptoms of toxicity may not be temporally related to exposure. Lead has no physiological role and is neurotoxic via several different mechanisms, including interfering with the electron transport chain. In many respects, chronic lead toxicity mimics porphyria because it inhibits aminolevulinic acid dehydratase and ferrochelatase, two enzymes of the haem biosynthesis pathway.

Acute lead exposure in adults causes lethargy, headache, confusion, impaired motor function and ataxia. Cerebral oedema may develop at higher concentrations. Chronic lead exposure manifests subtly and non-specifically and is notoriously difficult to recognise and diagnose. Mild cognitive impairment and behavioural changes may be the only initial complaints. Arthralgia, abdominal discomfort, constipation and blue gingival lead lines are all clues to the diagnosis. An accompanying peripheral motor-predominant neuropathy (discussed later) is highly suggestive.

In blood, lead is found predominantly in erythrocytes. Whole blood lead concentrations reflect non-sequestered lead and are, therefore, an indicator of acute exposure. A blood concentration of $\geq 10\,\mu g$/dL (in adults) is abnormal and should be investigated further. In 95% of the adult population, the blood concentration is less than $4.6\,\mu g$/dL.[8] In chronic exposure, blood lead concentrations may be normal but it is almost universal to find a microcytic, hypochromic anaemia with basophilic stippling.[9] Evidence of disturbed haem metabolism is also supportive, particularly elevated zinc protoporphyrins. X-ray fluorescence of bone is useful in chronic exposure but not currently the standard of care in the UK. NCSs can assist diagnosis and are discussed below.

Treatment involves removing the source of any ongoing lead exposure (eg, if ingested). At blood concentrations above $70\,\mu g$/dL, chelation with sodium calcium EDTA or 2,3-dimercaptosuccinic acid (DMSA or succimer) may be appropriate.

Inorganic and elemental mercury

Mercury is an ancient neurotoxin and exists in elemental, inorganic and organic forms. Generally speaking, mercury neurotoxicity manifests differently depending on its form.[10] Encephalopathy is predominantly associated with exposure to inorganic or elemental mercury. In contrast, organic mercury causes a cerebellar syndrome and peripheral neuropathy, discussed below. Elemental and inorganic mercury cross into the brain more slowly than organic mercury (which is actively transported) and is minimally absorbed from the gastrointestinal tract. Exposure to elemental mercury tends to be from occupational inhalation of mercury vapour, for example, in laboratory workers. The potential dangers of dental amalgams containing mercury have been a controversial topic, but there is currently no evidence that they cause neurotoxicity.[11] Various industrial processes risk exposure to inorganic mercury, which is also an ingredient in some traditional herbal remedies and skin-whitening preparations. Once in the central nervous system, mercury specifically targets grey matter. Chronic exposure to inorganic or elemental mercury classically causes emotional lability (excessive shyness and timidity with irritability) associated with gingivitis and tremor, typically a fine tremor with intermittent episodes of coarser tremor and myoclonus, occurring both at rest and on action. The condition was called ‘erethism mercurialis’ or ‘mad hatter syndrome’ due to 19th century mercury use in making felt for hats. The term ‘mercurial’ refers to someone liable to changes in mood, as in chronic mercury toxicity, which may be a coincidence or reflect the liquid nature of mercury that gave it its alternative name ‘quicksilver’. Renal dysfunction and mucosal damage are further clues to inorganic or elemental mercury toxicity.

The diagnosis of inorganic or elemental mercury toxicity is made by urinary testing (either random or 24-hour collection). This is in contrast to organic mercury for which blood is preferred, as discussed below. Urinary mercury concentrations reflect exposure over the previous 2–4 months. The background reference range for urinary mercury is $<1.4\,\mu mol$/mol creatinine, but neurological symptoms are unlikely below around $17\,\mu mol$/mol creatinine.

In severe exposure, chelation therapy may be appropriate with either DMSA or 2,3-dimercaptopropane-1-sulfonate (DMPS).

Leukoencephalopathy

In toxic leukoencephalopathies, white matter tract involvement leads to prominent neurobehavioural deficits and, in severe cases, a subcortical dementia. Cortical functions, such as speech and praxis, are typically spared.[12] The severity of the clinical deficit usually reflects the extent of white matter involvement, which is typically diffuse and widespread. Leukoencephalopathy in an industrial or occupational context is most often caused by organic solvents, which are lipid soluble and specifically target fatty myelin.

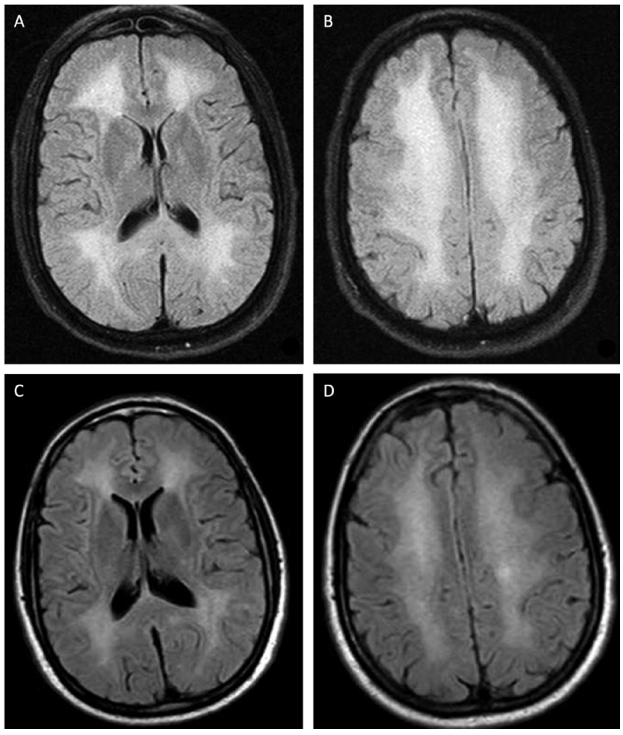

Figure 2 MR scan of brain. Axial FLAIR sequence of a man in his 40s who was a salesman of toluene-containing solvents. Images show diffuse confluent T2w/FLAIR signal hyperintensity indicating widespread white matter involvement at presentation (A) and (B). Some improvement was seen 6 weeks later, (C) and (D) when he had returned to behavioural and cognitive baseline. From: Qureshi *et al*.[41] Reproduced with permission from Cambridge University Press. FLAIR, fluid-attenuated inversion recovery.

The toxic effects of organic solvents were first described in Swedish painters (although subsequently referred to as Danish painters' syndrome) forced to retire early due to neurobehavioural symptoms.[13] However, organic solvents are used in a wide range of professional and domestic contexts and may also be drugs of abuse. Most industrial organic solvents are mixtures of multiple hydrocarbons, but the most important component is usually toluene, the toxic effects of which have been particularly well described. Prolonged toluene exposure results in multifocal leukoencephalopathy which, especially in younger adults, may initially be mistaken for multiple sclerosis. The resultant syndrome is characterised by dementia, ataxia and brainstem involvement.[14] In common with most solvents, the effects of toluene neurotoxicity may abate rapidly after stopping the exposure, which can result in the diagnostically useful phenomenon of transient improvement during the weekends in those exposed occupationally.

There are no specific diagnostic tests for organic solvent neurotoxicity, but imaging is often highly suggestive. White matter changes are readily seen as widespread, bilateral, periventricular and subcortical hyperintense signal on T2 and fluid-attenuated inversion recovery (FLAIR) MRI (figure 2). In common with several other toxic leukoencephalopathies, subcortical U-fibres are relatively spared. T2 hypointensity of the thalamus and basal ganglia may also occur, for reasons that are not fully understood. In general, toxic leukoencephalopathy is largely reversible and has a good prognosis following removal of the offending agent.

Cerebellar syndrome

The cerebellum is most commonly affected by alcohol and medications but is also the target of organic mercury. The cerebellar ataxia of organic mercury contrasts with the encephalopathy of inorganic and elemental mercury exposure. Neurotoxicity usually results from ingestion of fish or shellfish. Environmental mercury is converted into organic (usually methyl) mercury by micro-organisms in water and then accumulates in aquatic animals. Mercury biomagnifies in long-living predatory seafood such as shark, swordfish and bass. Perhaps the most infamous example of organic mercury toxicity was seen in Minamata Bay, Japan, where the industrial pollution of water for over 30 years resulted in neurotoxicity in several thousand people.[15] Symptomatically, ataxia and tremor are often accompanied by perioral numbness, visual field constriction (which can progress to cortical blindness) and length-dependent sensory neuropathy. Slurred speech may follow.[10] After acute exposure, there may be a delay of several months before these symptoms appear.

Unlike inorganic or elemental mercury, the diagnosis of organic mercury toxicity is the best made in whole blood. Not all positive results are clinically relevant. The typical upper limit of normal for blood mercury is around 5 ng/mL but clinical effects are very unusual below a concentration of 40 ng/mL.[8] Dental amalgams or fish-based diets can increase the blood concentration of mercury above the upper limit of normal but in a way that is not clinically significant. Mercury is especially susceptible to the phenomenon of pseudoneurotoxicity. It may not be best practice to perform a blood test in the absence of typical symptoms or a clear exposure to mercury; falsely positive results may cause unnecessary anxiety for both clinician and patient.

NCSs can be diagnostically helpful by confirming a length-dependent axonal polyneuropathy. Following prolonged exposure, MRI may reveal cerebellar atrophy (figure 3). DMPS or DMSA chelation therapy may be appropriate although most evidence for their efficacy comes from treating elemental or inorganic, rather than organic, mercury toxicity.

Parkinsonism

Our understanding of Parkinson's disease has been significantly advanced by the Parkinsonism-inducing neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydro pyridine (MPTP).[16] MPTP is used industrially as a

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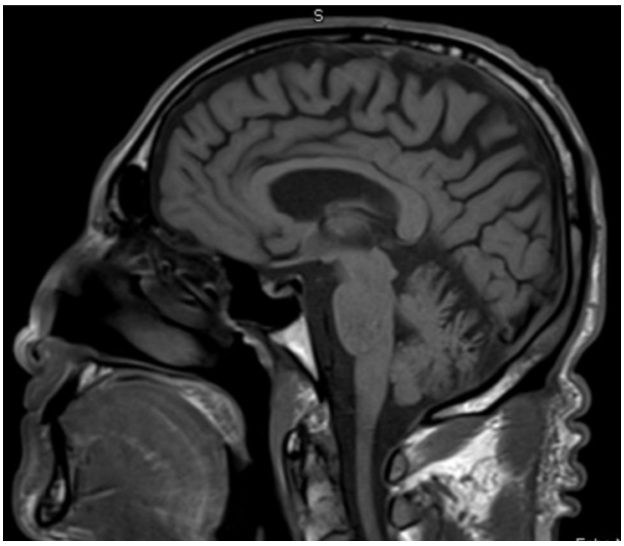

Figure 3 MR scan of brain. Sagittal T1 weighted image showing cerebellar volume loss in a man in his 60s who had eaten four cans of blended tuna every day for 25 years. From: Edwards and Powell.[42] Reproduced with permission from BMJ Publishing Group.

chemical intermediate but is perhaps better known as the accidental by-product of synthetic opioid manufacture that caused a profound Parkinsonian syndrome in several drug users in California in the 1970s. The environmental toxins most associated with parkinsonism are manganese, carbon monoxide and methanol.

Manganese

Manganism predominantly occurs in metalworkers and welders. It can also occur in people receiving long-term parenteral nutrition and in those taking homemade ephedrone, a stimulant that can be made from readily available cold medications using potassium permanganate. Manganese is deposited in the globus pallidi but largely spares the substantia nigra. The resultant reduction in the inhibitory GABA-ergic input to the subthalamic nucleus causes glutamatergic excitotoxicity in the substantia nigra. Several clinical features can help distinguish manganism from idiopathic Parkinson's disease. Neuropsychiatric, gait and balance difficulties are prominent and early manifestations. The gait of manganism is distinctive and sometimes described as a 'cock walk' due to pronounced plantarflexion and elbow flexion. Freezing is common and patients often have particular difficulty walking backwards. Dystonia is also more prominent than in Parkinson's disease. In contrast, tremor is mild and often absent, but when present is usually postural and bilateral. Bradykinesia and rigidity in manganese-induced Parkinsonism are also bilateral from early on in the disease course. There is usually no response to levodopa or only a limited and transient response.[17]

Manganese can be measured in whole blood, but the half-life is relatively short and concentrations reflect only recent exposure. Blood concentrations correlate only poorly with brain concentration and clinical severity. Blood is, therefore, a poor biomarker and the diagnosis usually relies on typical MR brain scan findings. Manganese deposition results in T1 hyperintensity in the globus pallidi bilaterally (figure 4) with normal T2 signal. This finding is a hallmark of manganese toxicity and distinguishes it from other metal deposition diseases such as neurodegeneration with brain iron accumulation.[18] However, MR brain scan evidence of manganese deposition alone does not necessarily imply neurotoxicity. Given the high prevalence of idiopathic Parkinson's disease compared with manganese-associated Parkinsonism, imaging changes must be combined with characteristic clinical findings to make the diagnosis.

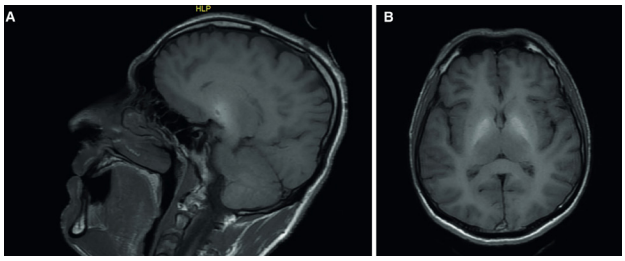

Figure 4 MR scan of brain. Sagittal (A) and axial (B) T1 weighted images of a manganese exposed welder showing signal hyperintensity in the globus pallidi bilaterally. From: Alici *et al*.[43] Reproduced under the terms of the Creative Commons BY licence.

Two chelation agents may be appropriate for manganese neurotoxicity: EDTA and para-aminosalicylic acid. These agents effectively reduce blood concentrations of manganese but have very little effect on clinical features of manganism.

Carbon monoxide and methanol

The characteristic bilateral pallidal necrosis of CO poisoning can cause a Parkinsonian syndrome (figure 1). As with CO encephalopathy, Parkinsonism is often delayed after exposure following an apparent period of partial recovery. Axial rigidity is prominent and the response to levodopa is poor. CO neurotoxicity is discussed in more detail above.

Methanol is produced by the improper preparation of ethanol but is also found in solvents and antifreeze. Encephalopathy and blindness (due to optic nerve oedema and necrosis) are usually the earliest signs of neurotoxicity, but the onset may be delayed while methanol is converted into the more toxic metabolite, formic acid. Methanol specifically targets the putamen and may cause parkinsonism. Methanol concentrations can be directly measured in blood (any value above 0 is abnormal) and there is usually also a raised anion gap metabolic acidosis. MR brain scan may show the classical finding of bilateral haemorrhagic putaminal necrosis. Early administration of the antidotes ethanol

or fomepizole helps to halt damage but will not reverse Parkinsonism or optic nerve damage once they have occurred. Some cases respond to levodopa.[19]

Peripheral neuropathy

Peripheral nerves are a common target for neurotoxins. Medications, including chemotherapeutic agents, are the most common cause and are the subject of other reviews.[20] Environmental peripheral nerve toxins include mercury, arsenic, lead, thallium, acrylamide, ciguatoxin and organophosphates. Mercury in its organic form (discussed in more detail above) can cause a length-dependent sensory neuropathy with prominent tremor.

Arsenic

Arsenic causes significant morbidity in those drinking contaminated groundwater. Exposure also occurs in the context of mining and smelting, and arsenic is an ingredient in some traditional Chinese and Indian medications. Deliberate poisoning is well described but rare. The neurological manifestations of arsenic neurotoxicity depend on whether the exposure is acute or chronic.[21] Acute exposure causes a diffuse sensorimotor neuropathy that clinically may mimic Guillain-Barré syndrome. The polyneuropathy may occur several weeks after an initial severe gastrointestinal illness, which can further confuse the diagnosis. Diarrhoea is often copious and watery. Cranial nerve involvement is uncommon. Unlike in Guillain-Barré syndrome, the neuropathy may be accompanied by encephalopathy, haematuria and jaundice. The patients' breath may have a garlic odour and they may report a metallic taste. Chronic arsenic exposure is the more common scenario. In contrast to acute toxicity, this usually causes a gradual-onset painful, length-dependent sensory axonal neuropathy. Dermatological manifestations are prominent and include a characteristic brown desquamation of the hands, hyperkeratosis and mucosal irritation. Mees' lines (white lines or bands across the nails) may also be seen. Accompanying gastrointestinal symptoms is a further clue to diagnosis.

Arsenic is rapidly cleared from blood so urinary testing is preferred. Total urinary arsenic is usually the first-line test, but this also includes measurement of non-toxic organic arsenic, found in seafood. Dietary organic arsenic can result in urinary arsenic concentrations up to several hundred times the upper limit of normal. Patients should, therefore, avoid seafood for 5 days ahead of testing to reduce the chances of a false positive result. In unexposed people, urinary arsenic is usually below 15 nmol/mmol creatinine. Inorganic urinary arsenic can be specifically requested as a second-line test. Urinary concentrations of arsenic remain elevated for several weeks, but when more remote exposure is suspected, nail and hair samples can be tested. These samples have the added benefit of being able to indicate the time of exposure, useful in forensic cases. NCSs can help in distinguishing acute arsenic toxicity from demyelinating forms of Guillain-Barré syndrome as they usually identify a sensorimotor axonopathy, although occasionally in severe toxicity there may also be demyelination.

DMSA and DMPS have a role in the management of both acute and chronic toxicity.[22] Following treatment and stopping exposure, the neurological symptoms may recover but this can be prolonged and often incomplete.

Lead

Lead is discussed more fully above in the context of encephalopathy. Lead neuropathy usually occurs due to chronic exposure in an industrial setting. Lead preferentially affects the radial nerve and the classical first symptom is weakness of wrist and finger extension. A more widespread motor-predominant neuropathy may follow. Less commonly, very prolonged exposure may cause a sensory neuropathy. Electrophysiological studies show axonal injury with reduced amplitude compound muscle action potentials, normal or mildly slowed motor conduction velocities and mildly prolonged distal latencies. Evidence of denervation is characteristic, including fibrillation potentials and polyphasic motor unit potentials. The prognosis of lead neuropathy is generally good after exposure has stopped.

Thallium

Thallium neurotoxicity is rare but has historically been favoured by those with homicidal intentions, as thallium salts are tasteless, odourless and often not detected on routine screens. Thallium is toxic via several mechanisms, including disruption of potassium-dependent processes. The rapidly progressive neuropathy associated with thallium is predominantly sensory. The neuropathy is usually length-dependent but cranial nerves may be involved. Severe pain is a significant feature and may be the earliest symptom. Alopecia, dysregulation of the sleep-wake cycle and mild gastrointestinal disturbance are further diagnostic clues but are not universally present. Alopecia may be delayed for up to 14 days, by which time neuropathy may be severe. However, inspection of hair roots identifies a dark discolouration as early as 4 days postexposure. The preferred diagnostic test is urinary thallium concentration. Below 5 μg/L is normal and above 20 μg/L is considered toxic. Blood and hair testing are also possible but less reliable.

A mainstay of treatment for thallium toxicity is Prussian blue, which binds to thallium and promotes its excretion via the bowel. Prussian blue should be given until thallium can no longer be detected in faeces.

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Acrylamide

Acrylamide monomer has the industrially useful property of polymerising into a stiff, waterproof gel. It is used in the manufacture of adhesives, grouting and in several other industries. The monomer, but not the polymer, is neurotoxic. On more than one occasion, an epidemic of acrylamide neurotoxicity has been associated with large-scale tunnelling operations. Acrylamide causes a length-dependent sensorimotor neuropathy with prominent sensory ataxia. Diagnostic clues include redness, hyperhidrosis and exfoliation at the site of absorption (usually the hands). Acrylamide reacts with and binds to haemoglobin molecules, forming acrylamide haemoglobin 'adducts'. The diagnosis of acrylamide toxicity is confirmed by finding these acrylamide haemoglobin adducts in blood, though this test is not widely available and normal ranges have not been established. Acrylamide haemoglobin adduct concentrations vary widely in the general population, probably due to dietary exposure, and can be significantly raised in smokers even without industrial exposure. One study found that 39% of exposed workers with concentrations over 1 nmol/g developed peripheral neuropathy.[23] NCSs show an axonopathy. Histopathologically, acrylamide neuropathy is characterised by distal-predominant axonal swelling due to neurofilament accumulation.

Removal from sources of acrylamide is the only specific treatment, following which neuropathy may slowly improve but often with residual deficits, especially sensory ataxia.

Ciguatoxin

Ciguatoxin is produced by the dinoflagellate plankton *Gambierdiscus toxicus* and is ingested by small reef fish. Ciguatoxin biomagnifies up the food chain and concentrates in fish such as red snapper, grouper and barracuda. Ciguatoxin is resistant to freezing and cooking and can persist even in imported fish. The disease that results from toxin ingestion, ciguatera, therefore, occurs over a wide geographical area, not just the Caribbean, Pacific Islands and the USA, where it is an endemic cause of peripheral neuropathy. Ciguatoxin binds to voltage-gated sodium channels, maintaining them in the open state and resulting in depolarisation and spontaneous activity. Ciguatera is characterised by acral and perioral paraesthesia, with pruritus developing 12–48 hours after ingestion. Hot–cold reversal and cold allodynia are highly characteristic. Weakness is rare. There is no specific diagnostic test, but neurophysiological studies may show generalised slowing and prolonged F waves.[24] There are no specific treatments beyond managing the neuropathic symptoms. Mannitol has been suggested as an effective treatment, based on several case series and an unblinded trial[25] but overall the evidence is inconclusive.[26] The neuropathy can persist for a long time after ingestion causing significant morbidity.

Organophosphates

Organophosphates are predominantly associated with autonomic features, described below, but exposure to certain organophosphates can result in organophosphate-induced delayed neuropathy, occurring 1–3 weeks following exposure. Organophosphate-induced delayed neuropathy most often occurs in agricultural workers, particularly sheep-dippers, exposed to organophosphate pesticides. The underlying mechanism is thought to be inhibition of neuropathy target esterase. Some organophosphates responsible for the delayed neuropathy, such as triorthocresyl phosphate, inhibit neuropathy target esterase but not acetylcholinesterase (AChE) so typical autonomic features may not always precede the neuropathy. Organophosphate-induced delayed neuropathy is a lower-limb predominant, sensorimotor polyneuropathy. A high-stepping gait may occur, with a flaccid paralysis in severe cases. In very severe cases, spinal involvement results in irreversible pyramidal signs. NCSs show that organophosphate-induced delayed neuropathy is an axonopathy. Recovery is variable and may be prolonged but can be complete if there has been no spinal involvement.

Myopathy and neuromuscular junction dysfunction

Medications are the most common causes of toxic myopathy. However, snake venom can be profoundly myotoxic as well as acting as a neuromuscular blocker and is discussed here. Botulinum neurotoxin (BoNT) is discussed as a toxin of the neuromuscular junction because environmental exposure can occur, and it has long been feared as a potential biochemical weapon.

Botulinum neurotoxin

BoNT is produced by the anaerobic bacillus *Clostridium botulinum*. There are eight BoNT serotypes (A–H), all of which bind to structures on the presynaptic motor neurone membrane. Common routes of exposure include direct ingestion in undercooked foods, spore inhalation and, rarely, therapeutic procedures. Iatrogenic botulism is predominantly associated with the off-label use of BoNT for weight loss, where it is injected into the stomach wall.[27] The practice of 'skin popping', where drugs of abuse are injected under the skin, may also be associated with botulism if contaminated needles are used.[28] Botulism usually starts with cranial nerve palsies, followed by a progressive paralysis. Symptoms onset may be delayed by several days following exposure. BoNT can also act at the cholinergic synapse. Symptoms of reduced parasympathetic activity, including dry mouth and dilated pupils, can help to differentiate botulism from other causes of neuromuscular weakness. Botulism may strongly resemble the Miller Fisher syndrome and although pupillary dilatation is often thought to help differentiate the two syndromes, it is not universally present.

Botulinum toxin can be detected in serum or faeces, or *C. botulinum* may be isolated from faeces, wounds or food samples (see box 2). At least 10 mL of serum is required and should be sent before giving the antitoxin, but treatment should not be delayed while results are awaited. EMG shows reduced compound muscle action potentials with normal latencies and conduction velocities and normal sensory conduction studies. Single fibre EMG shows decrement in response to repetitive nerve stimulation at lower frequencies and increment at higher rates of stimulation (20–50 Hz).[29]

Snake venoms

Snakebite toxicity is rare in the UK but is increasing with the rise in exotic pet ownership.[30] Globally, snakebites represent a significant burden of disease. Snake venoms usually contain a mix of multiple different neurotoxins, but the two main paralytic toxins are α-neurotoxins, found in elapids (cobras and mambas) and β -neurotoxins, found in both elapids and viperids (vipers and rattlesnakes). In general terms, α-neurotoxins act postsynaptically, binding reversibly to nicotinic acetylcholine (ACh) receptors on muscle. β-neurotoxins bind irreversibly to presynaptic motor nerve terminals and block acetylcholine release.[31] Muscle weakness usually involves levator palpebrae first, with ptosis the most common initial sign. Ophthalmoplegia, facial and bulbar weakness follow, and limb weakness may occur only in very severe cases. Respiratory muscles involvement is common and potentially fatal.

The venom of several snakes, particularly those from the viperid family, is profoundly myotoxic and can cause widespread muscle necrosis, associated with raised serum creatine kinase and myoglobinuria. Snake venoms may also be associated with coagulopathy, which can be a clue to the diagnosis. Supportive management is critical and prolonged ventilation may be required. Antivenoms, where available, are highly effective and clinicians should seek specialist advice to guide their use. Antivenoms are immunoglobulin fragments specific to a given venom but there are polyspecific preparations available. In general, by the time muscle weakness has developed, antivenoms have only minimal effect and are most effective when given as early as possible.

Autonomic dysfunction

Organophosphates

Organophosphates are a key component of many pesticides and neurotoxicity is, therefore, most commonly seen in agricultural workers.[32] Acute toxicity is usually associated with accidents in the preparation of pesticide sprays, but exposure also occurs during their routine use. Pesticide use is often seasonal so training in the proper handling of pesticides may lapse.

Organophosphates irreversibly bind to and inhibit AChE. The structurally similar carbamates, also used as pesticides, bind to AChE reversibly. Termination of cholinergic signalling completely depends on the AChE-mediated breakdown of ACh in the synaptic cleft. Inhibition, therefore, leads to sustained activity at cholinergic synaptic junctions, with several subsequent effects. Activity at muscarinic junctions results in disproportionate parasympathetic activity, the so-called 'cholinergic crisis' characterised by excessive salivation, lacrimation, diarrhoea, vomiting, bradycardia and prominent miosis. Overstimulation of nicotinic receptors at neuromuscular junctions causes a depolarising block with muscle weakness and fasciculation. Effects on cholinergic signalling in the central nervous system may cause CNS depression. An 'intermediate' syndrome is seen in up to 40% of those poisoned with organophosphates (though rarely with carbamates). This syndrome is characterised by proximal weakness, including respiratory muscle weakness, developing 24–96 hours following exposure, and after resolution of autonomic symptoms. Finally, a delayed neuropathy can develop and is discussed above. Importantly, organophosphates represent a wide and varied group of different toxins, and so not all of the features described here are always seen, and the absence of one or more 'typical' features should not be overinterpreted.

AChE activity can be assayed in red blood cells and can help to make a diagnosis, though this is of limited use in the acute setting where prompt recognition and treatment is required. EMG can also help. A unique finding is a repetitive muscle response following a single stimulus, which disappears on repeated stimulation.[33] EMG can also identify the intermediate syndrome of organophosphate neurotoxicity, in which the characteristic clinical syndrome is combined with a decrementing response to repetitive nerve stimulation on single-fibre EMG.

Organophosphates are also a fundamental component of certain chemical weapons, the so-called 'nerve agents'. There are several chemically related agents, with varying degrees of toxicity. The earliest nerve agents, tabun, sarin and soman, were initially developed (though never used) by the German military during World War II. Agents have since been employed in several high-profile incidents, including the Iraqi attack on Kurdish civilians in Halabja in 1988, the 1994 Tokyo subway attack and in Salisbury in 2018. In this latter incident, the colourless, odourless, Soviet-era agent Novichok (Russian for 'newcomer') was used in a failed murder attempt, triggering a multiagency response and necessitating a large-scale decontamination effort.[34] The victims presented with the features of a cholinergic crisis and the diagnosis

was confirmed by measuring inhibition of cholinesterase activity in blood. Rapid toxidrome recognition was critically important[35] and all patients were managed with specific treatments. The primary aim of treatment was to counter excessive cholinergic effects with atropine, which binds to muscarinic postsynaptic membranes, blocking the autonomic effects of excess ACh. Hyoscine hydrobromide, which crosses the blood–brain barrier, was also used to treat central effects. Pralidoxime was given on the theoretical basis that it displaces organophosphate from AChE, although it also has antinicotinic effects and probably treated toxicity at the site of the neuromuscular junction. In addition to these targeted treatments, supportive care is also extremely important and mechanical ventilation is often required. Although exceptionally rare, suspected cases of nerve agent poisoning in the UK can be escalated using the contact details in box 2.

The effects of low-level, chronic organophosphate exposure are controversial. Failure of ACh signal termination has the potential to injure downstream neurones permanently via excitotoxic mechanisms. Several epidemiological studies have linked chronic pesticide exposure to an increased risk of developing Parkinson's disease[36] and there may be a genetic predisposition to this.[37] The mechanism is not understood but may involve ACh and glutamate-mediated excitotoxicity in the basal ganglia.[38]

Trichloroethylene

Trichloroethylene (TCE) is used as a degreasing agent, and in paints, solvents and glues. Exposure to contaminated groundwater may occur due to improper disposal of industrial waste. TCE was also used as an inhalational anaesthetic and is a drug of abuse. TCE is classically associated with bilateral trigeminal sensory neuropathy but can also cause other cranial neuropathies.[39] Autonomic neuropathy may be prominent, resulting in cardiac arrhythmias and hypotension. Chronic exposure to TCE is associated with a significantly increased risk of developing Parkinson's disease. In a large population-based cohort study, US veterans from the Camp Lejeune military base, where water supplies were contaminated with TCE (and other volatile organic compounds), had a 70% higher risk of developing Parkinson's disease compared with a similar cohort from a non-contaminated military base.[40]

CONCLUSIONS

Neurotoxicology is a large, diverse and rapidly developing field. Practising neurologists are highly likely to encounter patients with neurotoxic presentations. Despite the challenges posed by the sheer variety of different neurotoxic syndromes, most presentations are likely to be due to a relatively limited number of different agents. In addition, there are often several clues to assist the diagnosis. Diagnostic challenges include the interpretation of laboratory and other paraclinical tests, and the concept of pseudo-neurotoxicity. The systems-based approach outlined in this review is intended to assist general neurologists in recognising neurotoxic disease. In practice, clinical features are often not as neatly delineated as presented here. However, by approaching patients using the questions outlined in the introduction, and by recognising a limited number of the more common or important neurotoxic presentations, neurologists should be able to diagnose most of the neurotoxic diseases presenting to the non-specialist clinic. Neurotoxicology is currently an under-resourced subspecialty of neurology but with a clear role in improving the lives of patients. The field is expanding as we gain a better understanding of neurotoxins and their mechanisms of action. In parallel with precision medicine more generally, we are also developing an improved understanding of genetic predispositions to neurotoxic disease. Only by better recognition of neurotoxicity at presentation will we be able to manage patients appropriately, advance research effectively and improve our understanding of neurotoxic disease.

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Key points

- A limited number of different neurotoxins are likely to be encountered in neurological practice and these are associated with characteristic clinical features.
- The choice and interpretation of investigations is a significant challenge in neurotoxicology, as false positives and negatives are common; performing screening tests for neurotoxins in the absence of a typical clinical syndrome risks false positive results, whereas choosing an inappropriate diagnostic test risks a false negative result.
- Urinalysis is preferred to blood testing for neurotoxins that are rapidly cleared from blood, such as arsenic, inorganic mercury and thallium.

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