A woman in her thirties with cough, tremor, agitation and visual disturbances

In the 1970s, a woman who was then in her thirties contacted her doctor with intermittent respiratory ailments, increasing fatigue, agitation and visual disturbances. She developed a complex array of symptoms involving multiple organ systems. More than 30 years would pass before the likely cause of the symptoms was identified.

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The woman contacted her doctor owing to an intense cough, headache and increasing fatigue. The doctor found her to be agitated, anxious and disoriented. He knew her well and had previously regarded her as mentally strong and well-balanced. She was signed off sick from work and recovered after a few days.

A year later, she contacted the doctor again with similar symptoms, but this time with the addition of a metallic taste in her mouth, intermittent tremor, blurred vision and impaired colour vision. She thought that she had become a little forgetful, which had also been mentioned by her colleagues. The doctor referred the patient to an ophthalmologist who found normal visual acuity, alignment, intraocular pressure and visual field bilaterally. Colour vision was not tested.

Some of the patient's symptoms (headache, increasing fatigue, cough) are common in the population (1), whereas the combination of forgetfulness, visual disturbances and respiratory ailments is more unusual. The medical records give no indication as to why spirometry and PEF measurements were not performed, nor why the patient was not referred to a neurologist.

Several of the symptoms, including impaired memory and concentration, visual disturbances and tremor, may indicate a disorder of the nervous system. Demyelinating diseases such as multiple sclerosis and other early-onset neurodegenerative disorders may be relevant differential diagnoses.

The patient slowly improved and was back at work after a few weeks, but after a while experienced increasing cognitive difficulties in the form of fatigue, impaired concentration and memory and increasing visual impairment. She was referred to the psychiatric services but no signs of mental illness were found.

Four years after symptom onset she was registered as 50 % disabled, but continued to work part-time as a dental nurse. It is unclear why she was not referred to a neurologist, neuropsychologist or pulmonary specialist as part of her disability assessment. After a long period of sick leave she again gradually improved, but her symptoms worsened when she returned to work. This pattern repeated itself over the following years.

Fifteen years after symptom onset, the patient was referred to a neurologist owing to strabismus and muscle twitching. The neurologist described moderate strabismus and minor fasciculations in the throat, neck and arms. One year later the occupational health doctor referred the patient to a pulmonary specialist because of her recurrent respiratory ailments. Spirometry was normal and a metacholine challenge test proved negative. However, at that point the patient had been on full sick leave for several months; the pulmonary specialist therefore recommended PEF measurements following her return to work.

Two years later the patient was referred for an occupational health assessment. She had by then been working as a dental assistant for more than 20 years – with exposure to mercury during the preparation of amalgam. PEF measurements were carried out over 18 days and the results were evaluated by a pulmonary specialist. However, because the patient worked only three days consecutively, the data were inadequate. There is no information as to why the patient was not referred to a neuropsychologist, but it appears from the discharge summary that multiple chemical sensitivity (MCS) was suspected as an explanation for the patient's complex array of symptoms and her oversensitivity to odours. Two years after the initial occupational health assessment, she was granted a 100 % disability pension.

Multiple chemical sensitivity is a condition with symptoms from multiple organ systems, including headache, increasing fatigue and respiratory ailments that can be triggered by stimuli such as strong odours (2, 3).

Our patient also had visual disturbances, tremor and cognitive difficulties, which are not common in multiple chemical sensitivity and which should trigger suspicion of neuro-

logical disease. Fluctuating cognitive impairments concurrent with increasing fatigue may indicate a more serious neurological disease, such as multiple sclerosis. Tremor in a young person may be of the benign essential type. However, its presence in combination with neurological symptoms such as cognitive failure and visual disturbances raises the possibility of other neurodegenerative disorders, for example diseases of the basal ganglia, such as Parkinson's disease or Wilson's disease.

The patient was re-examined by an ophthalmologist, who detected a restricted field of vision and pronounced cortical exophoria (outwards strabismus). A cerebral CT at Rikshospitalet revealed a rough frontal surface relief with a prominent Sylvian fissure bilaterally; the CT scan was otherwise normal. Lumbar puncture revealed normal cells and a normal protein level with no monoclonal bands. There was no sign of the production of Borrelia antibodies in the cerebrospinal fluid or blood.

Two years later the patient took part in a research project at the University of Bergen on the cognitive effects of mercury exposure, which entailed a simplified neuropsychological assessment. While there is no overview available of the tests that were performed, the neuropsychologist described the results as showing mild impairments in memory and autonomic reactivity. Cerebral MRI revealed enlargement of the subarachnoid space in the frontal cortex and cerebellum and mildly reduced signal in the putamen. An ophthalmological examination using the Farnsworth dichotomous colour vision test showed impaired colour vision. The patient was referred to a neurologist, who concluded that the clinical examination and imaging results indicated central nervous system atrophy and basal ganglia pathology.

Some of the patient's symptoms, such as headache, cough and shortness of breath, decreased after she stopped working and were thus partially reversible, but this was not the case for the tremor, cognitive difficulties and visual disturbances. The patient applied to the Norwegian Labour and Welfare Administration to have her symptoms recognised as work-related, but was unsuccessful because multiple chemical sensitivity is not on the list of recognised illnesses.

The patient contacted a researcher at Lund University in Sweden who had conducted studies on the effects of mercury in animals. He sent the patient's MR images to Boston Environmental Hazards Center at Boston University in the USA. A neurologist there described significant non-age appropriate frontal atrophy and weak to moderate atrophy of the cerebellum.

The patient's MR images were evaluated by two experts, who independently found marked frontal and cerebellar atrophy. The basal ganglia changes were minor and were not picked up in this second analysis. Atrophy and basal ganglia alterations are non-specific findings, but have been detected in some individuals that have been exposed to mercury (4).

In 2007, the patient was referred for another occupational health assessment. It emerged that she had prepared amalgam in a small room with poor ventilation. From 1969 to 1984 she had heated up copper amalgam up to 20 times a day. After 1984 she handled copper amalgam less often, but still regularly. She had also been exposed to mercury from silver amalgam daily until 1992. In 1993 the patient's renal function was normal and her urinary mercury concentration was 3 nmol/l (normal range < 50 nmol/l).

Occupational health specialists concluded that the mercury exposure was sufficient to produce a toxic encephalopathy and referred the patient to a neuropsychologist, who found reduced sensorimotor and psychomotor speed, impaired concentration, and memory in the lower range of normal. The patient was then referred to a neurologist for differential diagnostic clarification. The neurologist reported a somewhat atypical tremor, but that the clinical neurological examination and family history did not suggest any other underlying organic brain disorder and supported the diagnosis of toxic encephalopathy.

Discussion

This case history is based on retrospective review of medical records and information from the patient. It provides limited information on the diagnostic judgements and treatment-related choices that were made at the various times. The patient had early symptoms that are typical of mercury exposure: cough, fatigue, agitation, a metallic taste in the mouth, tremor, impaired memory and concentration. Visual disturbances were also a prominent symptom.

The patient's urinary mercury levels were not measured during her exposure, but a detailed review revealed that she was probably exposed to high concentrations of mercury vapour, particularly in the early part of her career. More than 30 years passed before she received a probable diagnosis, allowing her the possibility of having her condition recognised as an occupational disease. Such recognition gives entitlement to compensation for permanent injury from the Norwegian Labour and Welfare Administration and from Occupational Injuries and Diseases Insurance.

Copper amalgam contains about 70 % mercury and 30 % copper, and has greater plasticity and better antiseptic properties than standard amalgam (silver amalgam). During the preparation of dental fillings made from copper amalgam, high levels of mercury vapour are released. The preparation of silver amalgam, which contains approximately 50 % mercury, does not involve heating and therefore involves the release of less mercury vapour. In 1981, the Norwegian Directorate of Health advised dentists to exercise great restraint in the use of copper amalgam. However, an informal survey conducted by the Norwegian Board of Health Supervision in 1994 showed that some dentists were still using copper amalgam at that time.

The average mercury exposure among dental workers was estimated to be approximately 0.05 mg/m^3, which was the maximum permissible limit in Norway until 2007 (5). The old limit would on a group basis be equivalent to roughly 400 nmol/l (80 μg/l) in the urine (4). The half-life of mercury in the blood is 58 days (35–90 days) (4), but can be up to several years for mercury bound to nervous tissue (6). The mechanisms by which mercury affects the nervous system are largely unclear. It is known that Hg^{2+} is cytotoxic and may cause blockade of transmitter substances through binding to thiol or selenol groups in cell membrane proteins and enzymes (6) and that Hg^{2+} may affect neuronal architecture by binding to intracellular microtubules.

The results of urinary mercury measurements are available for one of the patient's colleagues, who performed the same duties at the same time as the patient. The measurements showed 59 μg/l, 18 μg/l and 15 μg/l. The Norwegian Institute of Occupational Health evaluated the results and concluded that they indicated exposure above the permitted limit.

It has long been known that exposure to mercury vapour may be neurotoxic and may impair renal function (4, 7), but that it may also cause visual impairments is less well known. In 2011, the Norwegian Knowledge Centre for the Health Services conducted a systematic review of mercury exposure among dental health personnel and concluded that these individuals were undoubtedly exposed to mercury, albeit to varying degrees (8). Studies of high methodological quality showed associations between urinary mercury and impairments in attention and memory, as well as poorer manual coordination. In 2012, Hilt et al. examined potential late complications among dental health personnel following mercury exposure; they concluded that while the incidence of such injuries is low, there is probably an increased

incidence of neurotoxic symptoms among dental assistants who worked with mercury amalgam (9). The research group also found mild impairment of visual memory in female dental health personnel.

Animal studies show that mercury accumulates in neurons, astrocytes and pyramidal cells and is deposited in the frontal and occipital lobes, and in the cerebellum, retina and optic nerve (4, 10, 11). Ellingsen et al. studied workers that had been exposed to mercury at a Norwegian chor-alkali plant (12), and concluded that reduced visually evoked potentials (VEP) in exposed individuals may indicate damage to visual pathways. Similar findings were obtained by Mathiesen et al., who demonstrated reduced visuomotor capacity among mercury-exposed chlor-alkali workers (13).

A study of dentists with low urinary mercury concentrations (5 µg/l) revealed reduced colour vision according to the Lanthony Desaturated D-15 Test and the Cambridge Colour Test, as well as tests of colour sensitivity (brightness, red–green and yellow–blue) (14). Several studies have confirmed that colour vision can be affected by moderate mercury exposure (14–18). Visual impairments are thought to occur earlier and with lower levels of exposure than other neurotoxic injuries (16–18). It is therefore likely that long-term exposure to low levels of mercury (urinary concentrations of roughly 40 µg/l) may have caused visual impairments in dental health personnel. Genetic variation and differences in exposure levels or vulnerability may explain why some are affected but not others (4, 14).

When neurotoxic damage is suspected, cerebral MRI should be performed and the patient referred to a neurologist. The neurologist will check for neurological impairments that may result from mercury deposition in different parts of the brain, and will rule out other neurological diseases. Specific testing of colour vision and visually evoked potentials should be carried out if the patient has visual disturbances. Chelation therapy (DMPS, alternatively DMSA) is appropriate for symptomatic patients with urinary mercury concentrations of 100 µg/l or above (19, 20). The chelator binds to mercury in the blood and reduces its binding to cellular structures in the brain if treatment is started quickly, preferably within four hours of an acute exposure (20).

The patient was eventually diagnosed with toxic encephalopathy on the basis of her characteristic symptoms and the objective results of neuropsychological and neurological assessments, and after specific colour vision tests and diagnostic imaging. Our conclusion was that the exposure was sufficient to produce the observed array of symptoms and had occurred in close connection with the onset of the patient's symptoms and ailments.

Many years after the exposure, the patient's urinary mercury concentration was within the normal range and treatment was no longer appropriate. The Norwegian Labour and Welfare Administration approved toxic encephalopathy, impaired colour vision and strabismus as an occupational disease, with permanent medical disability of 45 %. The patient also received compensation via the employer's Occupational Injuries and Diseases Insurance.

Summary

Our patient had acute work-related symptoms that are typical of harmful exposure to mercury, but more than 30 years went by before she received a probable diagnosis. The case history serves as a reminder of the importance of asking whether symptoms arise or worsen when the patient is at work. On suspicion of work-related symptoms, there should be a low threshold for referral to a specialist for diagnostic clarification and to an occupational health specialist for evaluation of exposure.

That mercury exposure can cause visual impairment is not well known. Testing of colour vision and neurological testing including visually evoked potentials should be carried out upon suspicion of visual impairment in persons that have been exposed to mercury.

In our patient the chronification of symptoms and development of permanent disability could probably have been avoided had her exposure been stopped earlier. Although the use of mercury in dental fillings has now been banned in Norway (since 2008), similar arrays of symptoms may occur upon exposure to other toxic substances, such as lead or organic solvents.

The patient has consented to the publication of this article.

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