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Pitfalls in clinical assessment of neurotoxic diseases: Negative effects of repeated diagnostic evaluation, illustrated by a clinical case

Moniek van Hout [a,*], Gerard Hageman [b], Evelien van Valen [c]

[a] Department of Medical Psychology, Medisch Spectrum Twente Hospital, Enschede, The Netherlands
[b] Department of Neurology, Medisch Spectrum Twente Hospital, Enschede, The Netherlands
[c] Netherlands Center for Occupational Diseases, Coronel Institute of Occupational Health, Academic Medical Center, University of Amsterdam, The Netherlands

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ABSTRACT

Exposure to different toxic substances can have acute and chronic neurological and neuropsychiatric health effects on humans. Patients often report impaired concentration and memory, irritability, fatigue, instability of affect and difficulties in impulse control. The diagnostic process for neurotoxic diseases is complex and relies heavily on the exclusion of differential diagnosis and substantiating the cognitive complaints by neuropsychological assessment. Diagnostic evaluations have the purpose to help the patient by finding an explanation for the symptoms to guide treatment strategy or prevent further deterioration. But what if the diagnostic process in itself leads to problems that can be quite persistent and difficult to manage? The iatrogenic, or sick-making, side effects of the diagnostic process are the main focus of this case study.

1. Introduction

Many workers are occupationally exposed to neurotoxic substances such as organic solvents, heavy metals or pesticides. Work related exposure to neurotoxic substances can have acute and chronic neurological and neuropsychiatric health effects on humans. Acute neurotoxic symptoms are for example nausea, headache, tiredness, light-headedness, feelings of drunkenness, concentration difficulties, euphoria, irritability, and slowed reflexes (Mergler, 2011), whereas chronic neurotoxic symptoms may consist of cognitive problems (especially in concentration and memory), irritability, fatigue, instability of affect, difficulties in impulse control, and parkinsonism (Elbaz et al., 2009; van Hout et al., 2006; Ross et al., 2013; Spurgeon, 2001; White and Proctor, 1997). Symptoms may vary with different neurochemical properties of the exposure and the duration and dose of the exposure. The classification made by the WHO (WHO, 1985) provides a framework for the neurotoxic effects of organic solvents, but might also be useful for diagnosing encephalopathies due to other neurotoxic substances.

Diagnosis of toxic encephalopathy is often complicated. Ideally, the diagnostic process has the purpose to help patients. If there are any problems caused by toxic hazards, patients should be advised regarding to safer work environment. However, the diagnostic process in itself may lead to problems that can be quite persistent and difficult to manage. We pose that the diagnostic process may have iatrogenic, or sick-making, side-effects, and will present a case history to illustrate this.

Although we present a patient with alleged chronic solvent-induced encephalopathy (CSE), our description of side-effects of the diagnostic process might apply to neurotoxic syndromes in general.

Martin's case

Martin is a 50-year-old male worker. His medical history is normal. His level of education is lower occupational, no learning or developmental problems are reported. Before 2002 he has had several jobs, without neurotoxic exposure. He was

* Corresponding author at: Department of Medical Psychology, Medisch Spectrum Twente Hospital, P.O. Box 50 000, 7500 KA Enschede, The Netherlands. Tel.: +31 53 4872822x2830; fax: +31 53 4872894.
E-mail addresses: m.vanhout@mst.nl, moniekvanhout@gmail.com (M. van Hout).

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unemployed several times for periods of one month through a year. Since 2002 until his sick leave in 2007, he worked in a distribution center of chemical products. He had to fill containers with chemical waste products, and to clean machines. He was daily exposed to hazardous materials and solvents, such as acetonitrile, benzene, acetone, toluene, xylene, and formaldehyde. According to Martin, safety regulations were often violated, and there were three incidents with peak exposure with acute complaints of headache, sickness and vomiting while mixing solvents. One incident was traumatic: he got solvents in his eyes, and suffered from transitory cornea damage.

In 2007 he presents to his GP with chronic headache, fatigue, and memory and concentration problems. He is edgy, down and feels apathetic. His complaints started after the first incident, and are progressive, even though he is on sick leave after another incident. Martin is worried sick about the safety of his work environment. He is referred to a neurologist in a nearby general hospital.

2. Diagnosing CSE

Over the years, several consensus based diagnostic criteria for CSE have been proposed (WHO, 1985; Baker and Seppäläinen, 1986; European Commission, 2009; van Valen et al., 2012). In these consensus documents, the core steps of the diagnostic process are specified: first, there have to be relevant symptoms. Second, the exposure to neurotoxic substances should be verified and should be sufficiently high to cause neurotoxic effects. Third, a clear temporal relationship between the onset of symptoms and exposure should be established, and fourth, other medical and psychological causes for the symptoms of the patient should be ruled out.

While these criteria seem straightforward, this case presentation illustrates that clinical practice is often complicated.

The diagnostic process usually starts with identifying relevant symptoms. However, the symptoms associated with chronic exposure are nonspecific, and overlap to a considerable degree with for now medically unexplained and controversial syndromes such as fibromyalgia, chronic fatigue syndrome, whiplash injury complaints, and with mental health problems such as depression, burnout and posttraumatic stress disorder (van Hout et al., 2003b). Most patients describe fatigue, dizziness, headaches, concentration difficulties and memory problems. These symptoms have a high prevalence in primary care, and it is difficult to figure out their etiology.

For the second step, life time exposure to neurotoxic substances should be assessed. This assessment can be very difficult, especially in retrospect (Burstyn and Kromhout, 2002; Tielemans et al., 1999). Assessment heavily relies on self-report, and often, adequate data of biological workplace monitoring are lacking.

The reliance on self-report might also imply difficulties for the third step, assessing the temporal relation between exposure and symptoms, although a patients' medical history in combination with the occupational history might provide important information.

Fourth, other relevant diagnoses have to be excluded. This requires elaborate clinical assessment to exclude for example neurodegenerative disorders (e.g., Alzheimer's disease and Parkinson's disease), neurovascular disorders, sleep disorders, neoplasms (e.g., brain tumors and paraneoplastic symptoms), metabolic causes (e.g., avitaminosis, thyroid disorders), traumatic brain disorders, psychiatric disorders (major depression, chronic pain) or developmental disorders (ADD/ADHD, dyslexia, (nonverbal) learning disorders, and autistic spectrum disorders), but also neurotoxic effects due to alcohol and drug intoxication should be accounted for (European Commission, 2009; Furu et al., 2012; Kaukiainen et al., 2009; Keski-Säntti et al., 2010; Kim and Kim, 2012; van Valen et al., 2012; Visser et al., 2011). Regarding follow-up, most patient based studies are in agreement about chronic solvent-induced encephalopathy being a non-progressive disease in which no severe deterioration of functioning occurs after diagnosis (van Valen et al., 2009). However, epidemiological studies show that exposure to several specific neurotoxic agents, such as manganese (Racette, 2013; Goldman et al., 2012), pesticides (Pezzoli and Cereda, 2013), and trichloroethylene (Lock et al., 2013) has been associated with a higher probability of development of progressive neurodegenerative diseases, especially Parkinson's disease. In that way worsening of neuropsychological results over time may be consistent with exposure related disease.

Medical history Martin

Although he is concerned about the occupational hazards, Martin is referred to a neurologist in a nearby general hospital. Neurological assessment and routine lab are normal. On neuropsychological assessment he performs very slow on tests of information processing speed, and extremely poor on memory tests. There are, however, inconsistent results on tests and also between test performance and his presentation in the diagnostic interview. Moreover, he performs below advised cut-off values on symptom validity testing. The neuropsychologist concludes that neuropsychological testing is invalidated by "malingering" and that complaints are probably "functional", without a hypothesis regarding etiology. He advises psychological treatment and retesting after one year. He does not discuss his conclusions with Martin and his wife.

A year later, Martin presents for retesting and is seen by another neuropsychologist. In the interview, his speech is blurred, slow, and he seems to have word finding problems. His clinical presentation is far worse than a year before. On assessment he has worse test results on all cognitive domains, compared to a year earlier. The neuropsychologist considers dementia. Symptom validity tests are not included in the test battery, and aggravation of cognitive symptoms is not considered as a hypothesis. Martin is then, nearly two years after first presentation, referred to a specialized Alzheimer Clinic. Medical screening, behavioral observation, routine blood lab, magnetic resonance scans, and lumbar puncture to analyze cerebrospinal fluid, are all normal. For the third time he is subjected to neuropsychological assessment. On this investigation, too, he performs incredibly poor on the tests, including symptom validity tests.

In the final consultation by the Alzheimer Clinic, hypotheses regarding the psychological etiology of complaints are discussed with Martin and his wife: possibly there is aggravation of cognitive symptoms, due to the traumatic impact of the incidents. He is reassured by his neurologist that dementia is improbable, and that his problems might be relieved by cognitive behavior therapy. In fact, he is not relieved at all. In the next year he is repeatedly referred for psychological treatment,

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