Science Letters ISSN 2345-5463 – An International Triannually Journal

Case report
2018 | Volume 6 | Issue 2 | Pages 81-87

ARTICLE INFO

Received
June 02, 2018
Accepted
July 29, 2018
Published
August 10, 2018

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Keywords
Toluene exposure
Leukoencephalopathy
Coenzyme Q10
MRI

How to Cite
Alsharif AA, Khan AA, Tian XX, Want JM, Nasir F, Guo YJ. Reversible toluene-induced leukoencephalopathy in a worker with long term exposure: a case report. Sci Lett 2018; 6(2):81-87

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Reversible Toluene-Induced Leukoencephalopathy in a Worker with Long Term Exposure: A Case Report and Literature Review

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Abstract

Chronic psycho-organic syndrome was first reported in 1976 in long-term house painters. Toluene-induced leukoencephalopathy's manifestations range from inattention, memory dysfunction, neurobehavioral impairment, coma and even death. A 33-year old male automotive painter was brought to the clinic with memory decline, dizziness, and dull response occurring gradually over a period of time, but became more apparent one week ago when patient lost his way in a familiar environment while he was driving his car. Neuroimaging reveal white matter injury. The patient was admitted for one month and was started on coenzyme Q10 250 ml and coenzyme Q10 complex 100 IU in 100 ml 0.9% NaCl. He was also prescribed a six-month course of vitamin C 0.1 g, vitamin B complex 0.1 g, vitamin E 0.1g, and coenzyme Q10 tablets (Ubiquinone) 10 mg. The patient had significant improvement clinically and radiologically after receiving the proper medical treatment. Abstinence from toluene may slow the process of white matter alteration and prevents further neuropsychological deterioration in patients with toluene-induced leukoencephalopathy, but it may be more helpful if management includes neuroprotective agents and antioxidants. The co-administration of coenzyme Q10, vitamin B, C and E may be an effective treatment of toluene leukoencephalopathy. To our knowledge, this is the first report that describes reversible leukoencephalopathy caused by prolonged exposure.

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Introduction

Toluene (methylbenzene), as the principal component (60-70%) of thinner [1], is an aromatic hydrocarbon solvent that is widely used as a component of many paints, lacquers, glues, adhesives, inks, and cleaning fluids. It is also widely used in chemical industries [2]. Some individuals deliberately inhale toluene vapors to experience euphoria [3], while others may inhale it unintentionally. In abusers; instantaneous intoxication is achieved by sniffing, bagging, or huffing toluene-based inhalants [4]. Abusers are mostly adolescents with lower socioeconomic background [5]. Toxic toluene inhalation can result from occupational exposure. Thus, it is an important health issue for workers in industries involved with toluene-containing product [6]. Toluene's ability to cross the blood-brain barrier and damage the white matter is attributed to the fact that toluene is highly lipophilic [7]. Due to genetic polymorphisms, the damage and body response to inhaled solvents (as toluene) may differ from one individual to another, since some people may be more sensitive to the effects of inhaled solvents than others [8]. Mostly, vapor inhalants (as toluene) are metabolized by the cytochrome P450 (CYP) system of the liver [9]. In general, inhalants are not assessed when performing routine urine drugs screening. Abnormal non-toxicological laboratory results, as elevated liver enzymes, should increase the suspicion of inhalant abuse. Excretion of toluene in the urine presents primarily as the metabolite hippuric acid; however, the excretion of hippuric acid is usually completed within 24 hours after exposure, and thus, screening of urinary hippuric acid could assist in the diagnosis of recent and chronic toluene-based inhalant abuse in a clinical setting, although false-positive results may present in some individuals [10]. At the cellular level, chronic toluene administration leads to decrease in neurogenesis, increased apoptosis, and elevated oxidative stress (OS) in the brain [11]. Chronic toluene exposure was also reported to cause multifocal central nervous system (CNS) defects, including bilateral optic neuropathy [12] and other

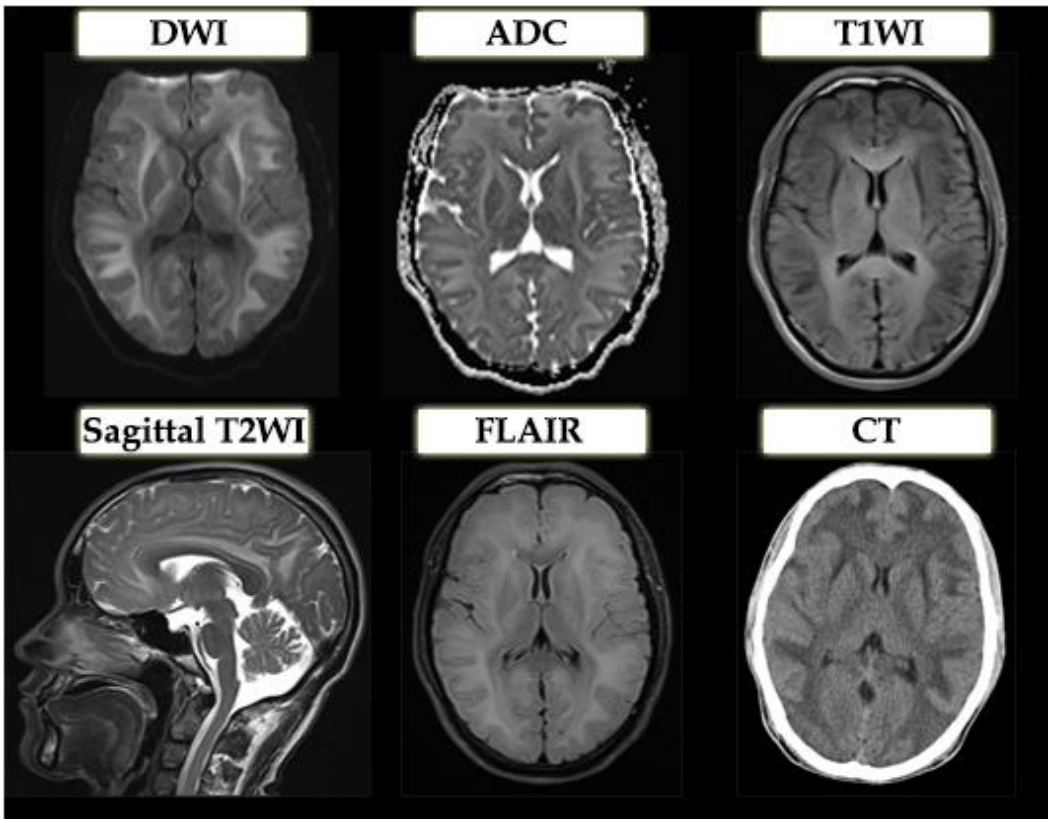

Fig. 1 Patient's imaging studies at the time of admission; Computed tomography (CT) shows that the gray-white matter differentiation is preserved, diffuse white matter hypodensity on both cerebral hemispheres. MRI demonstrates bilateral symmetrical abnormal signals in subcortical U-fibers, corticospinal tract (including internal and external capsules), corpus callosum, periventricular white matter and cerebellar dentate nucleus. MRI revealed no abnormal signals in cerebral grey matter, corona radiate, brain stem, and cerebellar hemispheres.

chronic health effects mainly against the CNS by pathological studies [13,14]. Chronic and intense exposure to this lipophilic-white matter toxin may result in a constellation of abnormal neuropsychological [15] and neuroradiological findings referred to as toluene-induced leukoencephalopathy [16, 17]. Here, we present a case of toluene‐induced leukoencephalopathy, with a 15-year history of toluene exposure that are presented with characteristic findings on computerized tomography scan (CT) and magnetic resonance imaging (MRI), which was reversed after abstinence from toluene exposure plus using neuroprotective and supplemental treatments.

Case report

A 33-year old male automotive painter, presented to the clinic with memory decline, dizziness, and dull response occurring gradually over a period of time, but became more apparent one week ago when he lost his way in a familiar environment while he was driving his car. The patient used to work in paint factory since he was 18 years old, and started working at an auto body garage 7 months prior to admission to our hospital. The patient had approximately 8 hours of daily exposure to toluene-containing paint thinner. The patient had no history of diabetes, hypertension, smoking, or alcohol consumption. His other past medical, surgical and family histories were noncontributory.

On physical exam, the patient looked slim (BMI=17.21 kg/m^2). His vital signs were within normal limit. Neuropsychological examination revealed memory decline, cognitive impairment, impaired calculation, impaired judgment, apathy, and a mini‐mental state examination (MMSE) score of 22. Cranial nerves, motor, sensory examination and deep tendon reflexes were all intact. Cerebellar function was normal, meningeal signs were negative. Physical exam was otherwise insignificant.

Laboratory evaluation showed normal blood cell counts, electrolytes, fasting blood glucose levels, liver and renal functions. Serum cortisol, adrenocorticotropic hormone (ACTH), ESR, hsCRP,

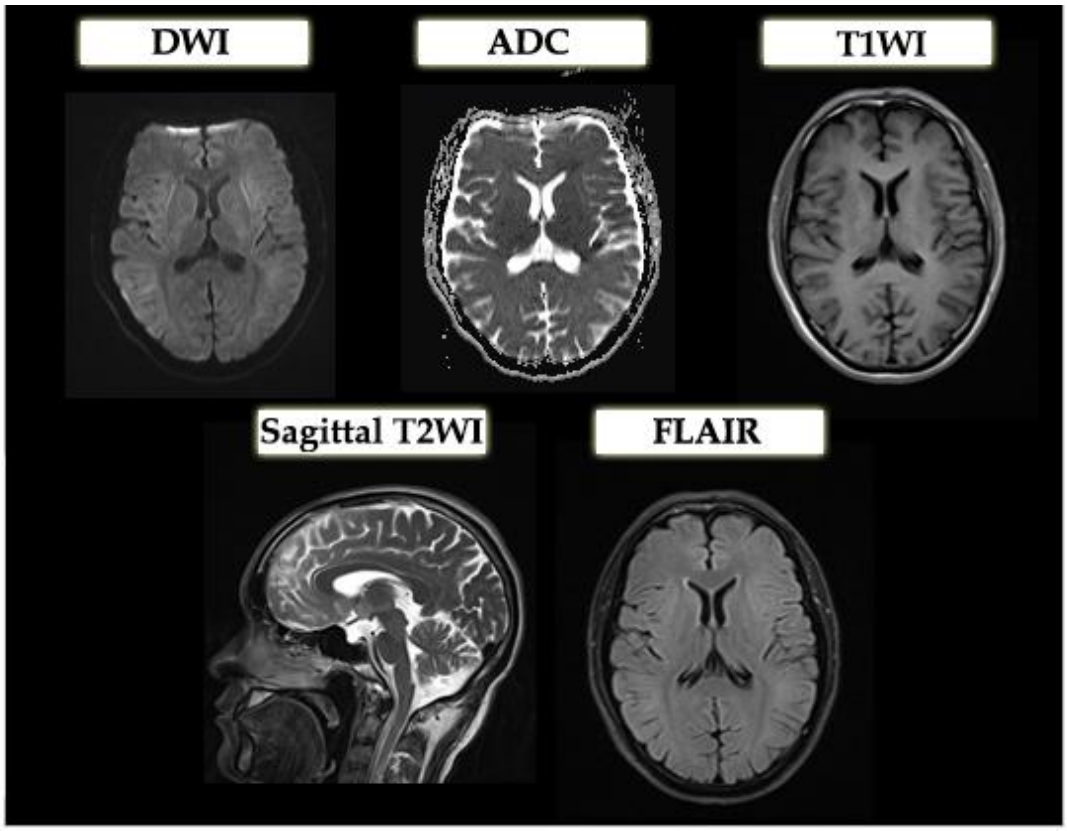

Fig. 2 Patient's imaging studies after three months of treatment; MRI shows great improvement compared to admission 3 months ago. MRI demonstrates decreased bilateral symmetrical abnormal signal in subcortical U-fibers, corticospinal tract (including internal and external capsules), and cerebellar dentate nucleus. MRI revealed no abnormal signals in cerebral grey matter, periventricular white matter, corona radiate, brain stem, and cerebellar hemispheres.

folic acid, vitamin B12, and ferritin levels were all The possibility of syphilis, hepatitis and human immunodeficiency virus infections were excluded. Lumbar puncture revealed a colorless and transparent adenosine deaminase (1 U/L) and CSF quantitative immunoglobulin G (19.8 mg/dl) were all normal. No oligoclonal bands of immunoglobulin G detected. The CSF total cell count was 0.410×10^9/L, white blood cell count was 0.002×10^9/L, red blood cell count was 0.408×10^9/L. No pathological cells were detected. CSF gram stain, cultures, and titers were all negative. Electroencephalogram and nerve conduction studies detected nothing unordinary. Brain CT showed diffuse white matter hypodensity on both cerebral hemispheres (Fig 1). Brain MRI studies, including transverse T1WI (T1-Weighted Imaging), T2-FLAIR (T2-fluid attenuated inversion recovery), DWI (diffusion weighted imaging), ADC (apparent diffusion coefficient), Sagittal T2WI, were all performed, and showed bilateral cerebral hemispheric white matter and cerebellar dentate nucleus lesions (Fig. 1).

After detailed clinical history taken from the patient and his family and careful physical examination combined with the radiological findings, the patient was diagnosed with chronic toluene leukoencephalopathy. The patient was admitted for one month and was started on coenzyme Q10 250 ml IV (qd) and coenzyme Q10 complex 100 IU in 100 ml 0.9% NaCl IV (qd). He was also prescribed a six-month course of vitamin C 0.1 g (tid), vitamin B complex (tid), vitamin E 0.1g (tid), and coenzyme Q10 tablets (ubiquinone) 10mg (tid). After treatment, the patient's symptoms were completely resolved, and a follow up brain MRI three months later showed significant improvement compared to the MRI obtained at admission (Fig. 2).

Discussion

Toluene-induced leukoencephalopathy is a structural alteration of the cerebral white matter, caused by sufficient dose and duration of exposure to toluene vapors resulting in damage to myelin [18], resulting in disturbances in higher cerebral functions, manifested as a spectrum of clinical features that range from inattention, memory dysfunction, visuospatial dysgnosia, dementia and neurobehavioral impairment to coma and may even cause death [7, 19]. Toluene-induced leukoencephalopathy requires 3 criteria for diagnosis: documented exposure to toluene, neurobehavioral deficits, and neuroradiological abnormalities. Neuroimaging and medical history are crucial for the within normal limits. Tumor markers were negative. cerebrospinal fluid (CSF). Intracranial pressure was 180 mmH_2O, CSF protein level (349 mg/L), glucose level (4.19 mmol/L), chlorine (119.5 mmol/L), diagnosis of the disease [19, 20]. Therefore, the presence of neuropsychological deficits with the absence of corroborating neuroradiological evidences supports the diagnosis of systemic disorders, such as hypothyroidism, hepatic encephalopathy, or uremia [19]. Head CT scan often shows only severe degrees of toxic leukoencephalopathy, such as marked demyelination or necrosis. It may also reveal cerebral cortical, cerebellar, and brainstem atrophy [19, 21]. An MRI may reveal cerebral cortical, cerebellar, and brainstem atrophy with sulcal widening and ventricular dilation [19, 22]. T2-weighted MRI is the imaging procedure of choice; because of its superior ability to display white matter. It usually shows widespread hyperintensities in the periventricular, subcortical and white matter regions of the affected patients [22]. As they concluded from earlier published articles, Gericke et al. [23] showed contradictory results in their published paper in 2001 by excluding the possibilities of chronic adverse health effects at very high toluene exposure levels. However, we disagree with this conclusion, as this study didn't include any radiological (imaging) findings (CT, MRI), and pathological or forensic (autopsy) results. However, their study was mostly limited to the clinical symptoms, ignoring the importance of radiological findings and ongoing pathological changes. Damage to the brain by toluene exposure was reported by others [24, 25]. Toluene-leukoencephalopathy and white matter injuries are supportive of our and others (Tables 1 and Table 2) conclusions that toluene inhalation may cause chronic health injuries, that is in contraindication with the conclusion brought by Gericke et al. [23].

The treatment of chronic toluene leukoencephalopathy includes abstinence from toluene and the administration of neuroprotective agents [16, 20, 21]. Regarding patient's recovery and prognosis, some of the previous studies [16, 20] reported partial or full recovery from symptoms but with no substantial MRI changes. Others reported worsening of symptoms with no improvement on MRI regardless of treatment [21, 26, 27]. However, one case report published by Qureshi et al. [28] showed brain MRI improvements after 6 weeks of abstinence from toluene with no medical treatment. It is worth mentioning that their patient was exposed to toluene for only 8 months, while ours had an 8-hour daily exposure to toluene for more than 15 years.

Table 1 Brain imaging findings, treatment and outcome and duration of exposure and abstinence from toluene in cases of toluene leukoencephalopathy in toluene abusers.

Brain Imaging findings/Other findings	Treatment/ duration of exposure and abstinence from toluene/ Outcome of the study:	Ref
(1) MR images showed diffuse white matter hyperintensity in the centrum semi-oval.	High-dose Solu-Medrol. Duration of exposure to toluene: Not available Duration of abstinence from toluene: patient continues inhaling toluene vapors. Outcome of the study: Recovery of symptoms: worsening neurologic status. Follow up MRI: MR Image 1 month later after continued toluene abuse shows extensive and progressive white matter disease Involving periventricular and capsular white matter and cerebral peduncles.	[26]
(2) A CT scan of the head revealed widened sulci, generalized cerebral and cerebellar atrophy and ventricular dilatation	Treatment: Abstinence from toluene for many years Duration of exposure to toluene: 23 years Duration of abstinence from toluene: many years Outcome of the study: Symptoms were worsened. Follow up MRI: Not available	[21]
(3) Brain MRI (1.5 T) revealed mild cerebral, cerebellar and corpus callosum atrophy, slightly increased signal in T2-weighted images in white matter and cerebellum and low signal in T2-weighted images bilaterally in dentate nuclei, red nuclei, substantia nigra, thalami, hypothalamic nuclei, caudate nuclei, globus pallidus, putamina.MRI showed mild leukoencephalopathy, but extensive hypointensities in T2-weighted images in basal ganglia, red and dentate nuclei, substantia nigra, thalami and hypothalamic nuclei. Other findings: This case provides the first DaT-scan results for presynaptic D2 dopamine receptors, which were found symmetrically decreased	Treatment: neuroleptics (olanzapine 5 mg 0–0–2). Duration of exposure to toluene: 10 years	[27]
(4) CT failed to reveal any abnormality. MRI: Cerebral atrophy is seen, most prominent in the corpus callosum and cerebellar vermis. There is generalized atrophy, loss of gray-white matter distinction, and diffuse paraventricular white matter high signal. Bilateral low signal foci are present in the caudate, putamen, globus pallidus, red nucleus, substantia nigra, and thalamus. In addition, low signal is seen in lobar gray matter. Mild low signal was also seen in the basis pontis bilaterally.	Treatment: Abstinence from toluene for 4 months Duration of exposure to toluene: 15 years Duration of abstinence from toluene: 4 months Outcome of the study: 4 months after abstinence from toluene led to improvement of visual symptoms Follow up MRI: MRI 3 years after presentation were unchanged	[16]

Thus, we suggest that the abstinence from toluene alone is not sufficient for the treatment of toluene leukoencephalopathy after long-term exposure, and the additional treatment with coenzyme Q10, neuroprotective agents and vitamins should be considered. As a result of our dual approach treatment, the patient's symptoms were completely resolved. A follow up brain MRI three months later revealed a great improvement and surprisingly most of the abnormal signals were faded away.

In addition to its function as a neuroprotective agent and an antioxidant [29, 30], CoQ10 can also recycle and regenerate other antioxidants, such as vitamins C and E [31–33]. Vitamin C supports the antioxidant activity of vitamin E [34–36], and recently was reported as an important agent in the treatment of inhalants intoxication [37]. Vitamin B group is involved in neuroprotection and prevention of cognitive decline [38]. Other reported nonconventional treatments include nigella sativa and methylene blue, which were recently reported to have a neuroprotective potential against the neurotoxic effects of toluene in experimental animals and may have a therapeutic benefit for patients with chronic toluene leukoencephalopathy [39, 40]. Stem cell therapy is also a promising therapeutic option for toluene leukoencephalopathy, by seeding glial or oligodendrocyte progenitor cells to achieve a proper remyelination [41].

Table 2 Brain imaging findings, treatment and outcome and duration of exposure and abstinence from toluene in cases of Toluene leukoencephalopathy in patients who had occupational exposure to toluene or had unintentionally inhaled the vapors.

Brain MRI findings	Treatment/ duration of exposure and abstinence from toluene	Outcome of the study	Ref
(1) MRI revealed diffuse cerebral white matter hyperintensity which resembled a characteristic "sunflower-like" change in T2-weighted images; it also showed symmetrical periventricular white matter hyperintensity in axial T2-weighted. Increased signal was visible in the cerebellar dentate nuclei. Gray matter-white matter differentiation was preserved.	Mannitol, hyperbaric oxygenation, intravenous ganglioside, GM1, Vitamins B12, B1, B6, huperzine-A tablets, and oxiracetam capsules. Duration of exposure to toluene: 3 years Duration of abstinence from toluene: 5 MONTHS	Recovery of symptoms: the patient's symptoms were mostly resolved, and at discharge; his MMSE was 26 Follow up MRI: not available	[20]
(2) MRI showed extensive, diffuse white matter changes. There were increased T2-weighted signal intensity throughout the subcortical and periventricular white matter	Quetiapine, 75mgs daily, for behavioral control Duration of exposure to toluene: 8 months Duration of abstinence from toluene: 5 MONTHS 6 WEEKS	Recovery of symptoms: after six weeks, his symptoms had fully recovered. Follow up MRI: (obtained after 6 weeks) MRI showed a reduction in the white matter changes although they persisted bilaterally in the periventricular region	[28]

Conclusions

Abstinence from toluene may slow the process of white matter alteration and prevents further neuropsychological deterioration in patients with toluene-induced leukoencephalopathy, but management of patients with neuroprotective agents and antioxidants such as the co-administration of coenzyme Q10, vitamin B, C and E might also be required. Further studies should be held in order to develop more effective therapies for this condition.

Abbreviations

Central nervous system (CNS)
Computerized tomography (CT)
Magnetic resonance imaging (MRI)
Body mass index (BMI)
Mini-mental state examination (MMSE)
Adrenocorticotropic hormone (ACTH)
Erythrocyte sedimentation rate (ESR)
High-sensitivity C-reactive protein (hsCRP)
Cerebrospinal fluid (CSF)
T1 Weighted imaging (T1WI)
T2-Fluid attenuated inversion recovery (T2-FLAIR)
Diffusion weighted imaging (DWI)
Apparent diffusion coefficient (ADC)
T2 weighted image (T2WI)
Coenzyme Q10 (CoQ10)
Intravenous (IV)
International unit (IU)
One time a day (qd) (Latin quaque die)
Three times a day (tid)

Consent

A written informed consent was obtained from the patient and his father for publication of this case report and any accompanying images. A copy of the written consent is available for the review of this article.

Conflict of interest

The authors declare that they have no conflict of interest.

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