

Epileptic seizures and occupational exposure to solvents: a cases series

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SUMMARY

Introduction: *Organic solvents (OS) are substances with well-known nervous system tropism. Long-term exposure can cause several neurological and neuropsychic manifestations (mainly toxic encephalopathy). A potential causal relation between epileptic seizures and exposure to OS remains controversial.* **Methods:** *We report seven cases of patients with no neurological history who had been professionally exposed to OS and who had at least one epileptic seizure after exposure. Selection of these cases was based on medical records of patients who were referred to the occupational health department of Charles Nicolle Hospital of Tunis during the period from January 1, 2010 to December 31, 2014.* **Results:** *Cases studied concerned five men and two women aged between 29 and 46. Professional seniority ranged from 2 to 31 years. In all cases, epileptic seizures occurred after exposure to a mixture of solvents. It was concluded, according to workplace inspections, that there was an important daily and direct OS exposure. Working conditions were considered as defective. Six cases had generalized seizures, one patient presented with status epilepticus. Illness onset occurred between one and nine years after the beginning of exposure to OS.* **Conclusion:** *These cases suggest a possible relationship between OS exposure and onset of epilepsy.*

RIASSUNTO

«**Attacchi epilettici ed esposizione a solventi**». **Introduzione:** *I solventi organici (SO) sono sostanze che provocano effetti tossici sul sistema nervoso. L'esposizione prolungata può causare gravi manifestazioni neurologiche e neuropsichiche, in primis l'encefalopatia tossica. Però, la potenziale relazione causale tra attacchi epilettici ed esposizione a SO rimane controversa.* **Metodi:** *Vengono presentati i casi di sette pazienti senza una precedente storia di disturbi neurologici, esposti a SO sul luogo di lavoro e che hanno sofferto almeno una crisi epilettica nel periodo di esposizione. I casi sono stati selezionati esaminando le cartelle cliniche dei pazienti giunti all'attenzione del dipartimento di medicina del lavoro dell'Ospedale Charles Nicolle di Tunisi nel periodo 1 gennaio 2010 - 31 dicembre 2014.* **Risultati:** *I casi analizzati riguardano cinque uomini e due donne, di età compresa tra 29 e 46 anni. L'anzianità lavorativa oscilla tra 2 e 31 anni. In tutti i casi, gli attacchi epilettici sono avvenuti dopo esposizione a una miscela di solventi. Sulla base dell'analisi dei rispettivi luoghi di lavoro, si è concluso che i lavoratori erano stati esposti quotidianamente e direttamente a SO. In sei casi vi sono state crisi epilettiche generalizzate, un paziente presentava status epilepticus. L'insorgenza delle crisi si è verificata da uno a nove anni dall'inizio dell'esposizione a SO.* **Conclusioni:** *Questi casi suggeriscono una possibile relazione causale tra esposizione a SO e insorgenza dell'epilessia.*

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INTRODUCTION

Organic solvents (OS) are widely used in industrial settings. Owing to their lipophilic properties, solvents have nervous system tropism. They are involved in the appearance of several neurological and psychic manifestations, essentially toxic encephalopathy (4).

Indeed, most epidemiological investigations conducted in occupational settings have demonstrated a direct relation between some neuropsychological diseases and occupational exposures. Exposure to chemical substances was the most reported. Knowledge about the occurrence of epilepsy after long-term OS exposure is mentioned in few reports.

We present a seven-case study of patients with newly diagnosed epilepsy in order to analyze the causal relationship between their long-term occupational exposure to OS and the occurrence of this neurological disease.

METHODS

This study was conducted in two stages. Firstly, it was a retrospective study collecting all the cases recorded by the occupational health center within the Charles Nicolle Hospital in Tunis during the period from January 1, 2014 to December 31, 2014. The study identified patients occupationally exposed to OS and who had had at least one epileptic seizure. Cases were registered by an intra-company occupational physician after being examined by the neurologist. Secondly, one year later, all those patients were invited to a check-out, during which missing information was collected, including disease progression and their occupational history.

Employees occasionally exposed to OS, patients who had a personal history of epilepsy, pathologies or head trauma that might be responsible for epileptic seizures as well as those who didn't complete the investigations were not included in the study.

Data were collected using a pre-established form containing socio-demographic medical reports (taken from the medical records of patients) and information gathered during the inspections at the workplaces performed by intra company occupational physician (qualitative assessment of OS ex-

posure). These medical data, collected by the same occupational physician after interviewing patients, were related to the date of onset of epileptic seizures, onset of exposure, the type and frequency of seizures and the progress of the disease after removing exposure. Screening for neuropsychological events was based on some findings, including the Q16 Swedish questionnaire (12). We also collected the results of the complementary investigations such as electroencephalogram (EEG) and brain imaging (brain computed tomography (CT) or magnetic resonance imaging (MRI)) performed in all cases.

Free agreement of all patients included in the study was obtained before the consultation of the medical records. During data collection and analysis, anonymity was respected.

CASE REPORTS

This study is about seven cases of confirmed diagnosis of epileptic seizures treated with antiepileptics. Personal medical history, history of neurologic disease, neuropsychic symptoms according the Q16 questionnaire, general work condition and use of personal protective equipment are shown in table 1. None of the cases had an extra-professional activity with a possible exposure to neurotoxic products. For all cases, neurologic examination revealed no abnormalities. Work place studies concluded that there was an important daily and direct OS exposure.

Case 1

A male polyvalent worker in a leather and shoes factory (shoe assembly unit) for seven years. He was assigned to a glueing station where he applied OS with a brush on the soles and the different parts of the shoes to be glued at a rate of seven hours a day.

The glue he used contained acetone, cyclohexanone, hexane, ethyl acetate, methyl ethyl ketone and toluene. The glue containers were often left open after use. Additionally, environmental exposure due to the presence of OS in near stations was noted.

Seven years after exposure to OS, he developed a first epileptic seizure at home upon return from work. MRI and post critical EEG were normal. A definitive removal from exposure to OS was rec-

Table 1 - Description of medical and professional characteristics of cases

Case	1	2	3	4	5	6	7
Alcohol consumption	-	-	-	-	-	-	-
History of Neurologic disease	-	-	-	-	-	-	-
Personal Medical history	-	Hypertension	-	-	Functional colopathy	-	-
Neuropsychic symptoms: Q16	Irritability, fatigue	Headaches, memory disorder	Headaches, irritability, memory disorder	-	Headaches, Depression fatigue, loss of libido	-	Headaches, fatigue, decreased libido
Personal protective equipment	-	-	-	-	+/-	-	+/-
Working conditions	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

-: Absence. +/-: Available but not used

ommended but not respected by the company. Six months later, the patient developed a second generalized seizure at the workplace. Therefore, he was transferred to another job with no exposure to OS. After six months, the patient declared disappearance of the seizures. Irritability and fatigue persisted.

Case 2

A female worker in a company manufacturing electrical appliances. She worked for 27 years in the spray painting and furnace enamelling department with a direct and daily exposure to OS vapors contained in painting products, resins and siccatives with exposure to heat. Then she was given a job as an operator on metal cutting machines for two years. Additionally, she was exposed to noise and OS from the near posts.

After 11 years of exposure she developed a generalized seizure. MRI was within limits. Post critical EEG showed generalized paroxysmal abnormalities, predominantly of the right hemisphere, to stimulation tests. A definitive removal from exposure to

OS was recommended and she was transferred to another post without exposure to OS. Seizures decreased and then disappeared three months later. Headaches and memory disorder persisted.

Case 3

A male worker in a company manufacturing car steering wheels. He worked for 10 years as an operator at the deburring-control station. His task was to clean car steering wheels with a mixture of OS and to control their quality. In addition, he was indirectly exposed to paint vapors, adhesives and thinner from the near posts. After six years of exposure, he experienced episodes of loss of consciousness at the workplace. MRI showed non-specific frontal cortical signal abnormalities and the post critical EEG was normal. A definitive removal from exposure to OS was recommended but not complied with by the company due to the absence of job reclassification. The employee continued to have seizures. Eventually, he decided to leave his job. Seizures and neuropsychic symptoms disappeared.

Case 4

A female worker in a company manufacturing car steering wheels. She worked in the car wheel wrapping unit for four years as a glueing operator. She was exposed daily to glues made of OS. After two years of exposure she developed three generalized seizures at the workplace. Brain CT and post critical EEG were without abnormalities. After removal from exposure to OS, seizures decreased and disappeared.

Case 5

A male worker in a metal industry company. He held for 13 years the job of sanding metal pieces, paint stripping by sandblasting or heat and spray painting metal parts (anti rust and lacquered). His work required a daily direct exposure to a mixture of OS found in painting products such as xylene, ethylbenzene and trimethylbenzene.

After six years of exposure he experienced episodes of loss of consciousness at the workplace with an increase in the number of crises. Then crises occurred at home upon return from work. The EEG detected epileptic form discharges and the brain CT were normal. A definitive removal from exposure to OS was recommended, but the company didn't comply. In spite of antiepileptic treatment, the patient continued to have epileptic seizures which became more frequent. Therefore, he quit his job, and epileptic seizures as well as neuropsychic symptoms disappeared.

Case 6

A male worker in a leather and shoes company for nine years. He worked three years in the stitching station and six years in the glueing and stitching station. He manipulated glues based on OS at a rate of two to three liters per day. After nine years of exposure he developed a status epilepticus. He was transported to a hospital. Brain CT was within limits and brain MRI showed a T2 hypersignal, flair and T1 bilateral and symmetrical lenticulars. Post critical EEG was normal. A definitive removal from exposure to OS was recommended but the patient quit the company. Seizures disappeared after removal from exposure to OS.

Case 7

A male printing operator in a printing house for 31 years. He manipulated various chemicals including inks, paint thinner and varnishes and filled the machine with six colors of ink (10 to 12 Kg of each color) and with varnish (25 Kg) every day. He used alcohol to clean the different parts of the machine and washed his hands repeatedly every day with paint thinner. After nine years of exposure he had two epileptic seizures at the workplace. Brain MRI and EEG were normal. A definitive removal from exposure to OS was recommended and the patient changed to another post. Seizures, headaches, fatigue and decreased libido disappeared after eliminating exposure to OS.

DISCUSSION

There is a rich literature on chronic encephalopathy related to OS. Nevertheless, other neuropsychiatric pathologies have been reported such as dementia (18) and epilepsy (13, 3, 23, 11). The link between chronic exposure to organic solvents and the occurrence of epilepsy remains controversial.

Some experimental studies have investigated the epileptogenic effect of certain OS. In a study investigating the epileptogenic effect of ethanol and propylene glycol on mice, a significant increase in the number of seizures was observed after repeated administration during four days (19). Another study about mice, in which varying doses of n-hexane, ethyl acetate and toluene were used, showed that n-hexane increases the severity of seizures induced by low doses of electroshock with no convulsive effect. Ethyl acetate produces generalized clonic seizures and death at high doses. Toluene induces clonic seizures of the forelimbs at high doses. (23)

In vitro studies performed on human cells exposed to a mixture of toluene, n-hexane and methyl ethyl ketone cell provided evidence of a cellular damage and biochemical alterations with an increase in free intracellular calcium after five days of exposure (14).

The link between ethanol or ethyl alcohol, which is an alcohol present in alcoholic beverages and also used as a solvent in industry, and epilepsy has been

known for a long time. It acts by lowering the epileptogenic threshold. The direct convulsive effect of alcohol has been associated with a change in local microcirculation and with hypomagnesaemia (10). Alcohol is the main cause of adult seizures (7). Indeed, it was observed that more than 40% of patients with seizures admitted to emergency department consumed high doses of alcohol. A direct and proportional relation between the risk of a first attack and the quantity of alcohol absorbed suggests a

dose-effect relation between alcohol and the risk of convulsion (17).

There are a few reports of epilepsy and OS exposure which describe only two cases (Table 2). In our report, we recorded seven cases of epilepsy in workers daily exposed to an important OS mixture. The cases of epilepsy described in literature were often related to exposure to a mixture of solvents in occupational settings (table 2). Occupational exposure to OS was often chronic, repeated and associated with

Table 2 - Synthesis of cases reported in the present study and cases reported in literature

	Number of cases	Sector of activity or profession	Solvents exposure	Type of intoxication	Type of seizure	Time to onset
Our study, 2018	7	Leather shoes factory Manufacture of electrical appliances Automotive industry, Metal industry, Printing	Mixture of organic solvents: Acetone, Cyclohexanone, Hexane, Ethyl acetate, methyl ethyl ketone and toluene, Xylene, ethylbenzene and trimethylbenzene	Chronic	6: Generalized seizures 1: Status epilepticus	from 1 to 9 years
Van Hooste, 2017 (24)	1	Paintbrush manufactory	Mixture of organic solvents: toluene, 2-butanone, n-Butyl acetate, ethanol, isobutyl alcohol, isopropyl alcohol	Chronic	Generalized seizures	24 years
Sanz, 2008 (21)	1	Leather shoes factory	Trichlorethylene	Chronic	Myoclonic encephalopathy	18 months
Ginja, 2007 (5)	1	Dry cleaning	Perchloroethylene	Chronic	Focal seizures	3 years
Mutez, 2006 (16)	1	Painter	Trichlorethylene (TCE)	Acute (voluntary inhalation of TCE)	Temporal seizure	-
Jacobsen, 1994 (9)	1	Wirter	Mixture of organic solvent: Cyclohexanone, Whit Spirit, Isopronalol	Chronic	Temporal seizure	10 years
Bernardini, 1992 (2)	2	Painters	Mixture of organic solvents	Chronic	Generalized seizures	10 years
Allister, 1981 (1)	1	Unemployed (glue sniffer)	Toluene	Acute (glue sniffer)	Status epilepticus	-

poor industrial hygiene conditions (2, 9) as in our seven cases. In addition, some authors have reported cases of epilepsy associated with acute and massive solvent intoxication (1, 16).

Onset of the disease in our cases ranged from one to nine years after the beginning of exposure to OS, it was variable in the cases reported in literature (more than one year) ranging between 18 months and 10 years.

In six cases our patients had generalized seizures and in one case they had a status epilepticus. These types of seizures occurred in the majority of cases in the workplace. For the cases reported in literature, the seizures were predominantly of a focal temporal type (9, 16, 5), one case of status epilepticus was reported in a solvent sniffer (1).

Trichlorethylene (TCE) was reported as one of the OS responsible for the genesis of temporal seizures. Indeed, several studies have reported cases of temporal seizures related to acute or chronic exposure to trichloroethylene (16, 21, 15). Temporal involvement is not clearly explained by the mechanism of action of these toxic products. However, several experimental studies performed on animals demonstrated a preferential neurotoxicity on the hippocampus and a modification of the neurotransmitters at the cerebral level (20, 22). Temporal localization is described in histological studies of the brains of gerbils and rats exposed to TCE (6, 8).

In our series of cases, post critical EEG recorded abnormalities in two cases. In literature, in the reported cases of temporal seizures, electro-encephalographic and neuroradiological abnormalities recorded solvent tropisms of the temporal lobe (9, 16).

The psycho-organic syndrome is mainly described during chronic intoxications; it is characterized by changes in personality (asthenia, emotional liability, depression, and apathy), headaches and vegetative disorders (sweating, giddiness, digestive disorders) as well as cognitive disorders (memory and concentration disorders, psychomotor retardation) (4).

The majority of clinical cases reported in literature found an association between epilepsy and the psycho-organic syndrome (2, 9, 16, 5). Six out of seven cases manifested this syndrome, supporting the thesis of the neurotoxic effect of organic solvents with central nervous system involvement.

The favorable course of the disease after removal from exposure reinforces the hypothesis of a probable toxic origin. For all our patients cessation of exposure to OS was prescribed. Progression of the clinical signs of the organic psycho-organic syndrome was variable. In all cases epileptic seizures disappeared when exposure stopped. In the cases reported in literature, removal from exposure led either to a disappearance of the attacks or a decrease in their frequency. (9, 16, 21, 24).

A synthesis of our study and the cases described in literature is reported in table 2 below.

CONCLUSIONS

Organic solvents are known to have neurotoxic effects. Our cases support the hypothesis of a chronological connection between OS exposure and epilepsy. However, it wasn't possible to identify a definite causal relationship.

Other epidemiological as well as experimental studies involving various solvents are needed to establish a strong and stable causal relation between epilepsy and exposure to organic solvents.

NO POTENTIAL CONFLICT OF INTEREST RELEVANT TO THIS ARTICLE WAS REPORTED BY THE AUTHORS

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