Non convulsive refractory status epilepticus induced by thiocolchicoside (TCC) intrathecal injection: A case report

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TCC is a semisynthetic molecule widely used in clinical settings as a pain killer and myorelaxant. Several neurological side effects have been reported in association with TCC treatment including somnolence, confusion and seizure, the latter in a lower percentage of patients. Some previous reports described seizure onset after TCC intake in adulthood. However, major epileptological complication, namely status epilepticus, has never been previously reported in association with TCC treatment. In our report, we describe a case of acute refractory non-convulsive status epilepticus (NCSE) in the context of a TCC-induced acute toxic encephalopathy (ATE) in a woman without any previous neurological or physical comorbidities.

KEYWORDS
acute toxic encephalopathy, amnesia, case report, non-convulsive status epilepticus, thiocolchicoside

1 | INTRODUCTION

Thiocolchicoside (TCC) is a semisynthetic molecule frequently used in humans for its muscle-relaxant as well as anti-inflammatory and analgesic effects. TCC is frequently used in the management of low back pain in association with non-steroidal anti-inflammatory drugs (NSAIDs). According to the literature, treatment with intramuscular TCC is effective and well-tolerated and its clinical efficacy and safety have been demonstrated in randomized double-blind clinical trials.1 TCC is an analogue of colchicine since they share the same benzo(α)heptalenic moiety.2

Even though the mechanism of action of TCC is not yet well understood, previous studies have suggested the interaction of this compound with a cortical subtype of the gamma-aminobutyric acid type A (GABA-A) receptor, inhibiting GABAergic transmission.3 This peculiar mechanism could explain its pro-epileptogenic properties. In fact, TCC was described to reduce seizure threshold and cause convulsions in rat models.4

In the present report, we describe a case of acute non-convulsive status epilepticus (NCSE) in a healthy adult patient with no previous history of epilepsy, brain injury or blood–brain barrier disruption after erroneous TCC intrathecal injection for the treatment of muscle contracture and low back pain.

2 | CASE REPORT

A 43-year-old woman was admitted to the emergency room complaining of the abrupt onset of cognitive motor-slowing, blurred vision, sensory deficits in her lower limbs followed by loss of consciousness. The patient’s recent as well as past medical history was unremarkable. No prior history of epilepsy, psychiatric comorbidities...
as well as a documented previous cognitive impairment was reported. The patient was not taking any home drug therapy.

Thirty minutes before admission, the patient was treated with an erroneous intrathecal injection of TCC, performed by her chiropractor, for lumbar muscle contracture and low back pain. At the physical examination, the injection site was extremely close to the patient’s L2 spinous process.

At first, the patient underwent a computed tomography (CT) of the brain which ruled out subdural haematoma, stroke or subarachnoid haemorrhage. A complete blood examination assessment (which included electrolytes, azotaemia, ammonia, glycaemia, and blood gas analysis) was performed, with all results within normal ranges. In the context of the emergency setting, according to the hospital local guideline, an electroencephalogram (EEG) with reduced montage (i.e., eight electrodes, four per hemisphere) was performed. EEG showed rhythmic high amplitude 2–3 Hz delta activity with superimposed diphasic sharp waves and spikes in the bilateral temporal derivations (Figure 1A). Thus, the patient was treated with an intravenous (i.v.) bolus of midazolam (MDZ) 10 mg with a sudden electroclinical improvement. According to Salzburg Criteria, 5 continuous

![Figure 1](image_url)

**FIGURE 1** Electroencephalogram (EEG). (A) High amplitude (150–200 \textmu V), 2–3 Hz delta activity with superimposed diphasic sharp waves and spike in the bilateral temporal derivations. (B) EEG performed by i.v. bolus of levetiracetam and lacosamide. (C) EEG performed after 2 weeks showed normal background alpha activity with sporadic 6–7 Hz slow abnormalities in the bilateral temporal derivations (Figure 1C)
(quasi-)rhythmic delta-theta activity with frequency >0.5 cycles per second, when associated with a clear clinical response, enables diagnosis of non-convulsive status epilepticus (NCSE).

The Naranjo Scale was used to assess the adverse reaction after intrathecal injection of TCC. A score of 6/13 was obtained, indicative of probable adverse drug injection reaction.

After 20 minutes, a subsequent worsening of the EEG was observed. In addition, constant pulse oximetry monitoring was performed, showing reduced partial pressure of oxygen (paO2) that, however, never went below 87%. Due to the risk of a worsening in respiratory function, additional benzodiazepines were not administered. Hence, an i.v. bolus of levetiracetam (LEV) 2000 mg and lacosamide (LCS) 200 mg was administered with a poor electroclinical response (Figure 1B).

Considering the lack of clinical response to the antiseizure treatment, the patient was transferred to the intensive care unit (ICU), where she was intubated and treated with propofol 2 mg/kg/h. A regimen of intravenous daily administration of levetiracetam (LEV) 3000 mg/day and lacosamide (LCS) 200 mg/day was set. To evaluate the electroclinical response, serial 60-minute EEG monitoring was performed every 24 hours. On Day 1, the EEG showed middle amplitude, 4–5 Hz slow abnormalities in the bilateral temporal derivations.

On Day 2, the patient underwent magnetic resonance imaging (MRI) of the brain which showed a non-specific bilateral periventricular hyperintensity (Figure 2A–2F). On Day 3, due to the EEG improvement, propofol therapy was discontinued, and the patient was transferred to sub-intensive care and discharged on Day 10, transferred to a rehabilitation clinic.

After the hospitalization, cognitive impairment was noted, with prominent attention deficits and retrograde amnesia (i.e., the patient declared not to remember the last 2 years). Folate and vitamin B12 deficiency, as well as hypothyroidism, were excluded. Afterwards, a comprehensive neuropsychological evaluation documented the presence of a single-domain amnestic mild cognitive impairment (MCI), with verbal and visual explicit memory deficits, along with working memory impairment (Table 1). The other cognitive domains (i.e., executive, visuo-praxis, language) were unaffected.

Two weeks later, a control EEG showed slow 6–7 Hz abnormalities in the bilateral temporal derivations (Figure 1B). A repeated brain MRI, performed after the hospitalization, confirmed the non-specific periventricular white matter abnormalities without signs of brain atrophy. A 3-month follow-up visit documented the persistence of cognitive dysfunction with a single-domain amnestic MCI, associated with verbal and visual explicit memory deficits.

3 | DISCUSSION

TCC is a semisynthetic molecule widely used in clinical settings as a pain killer and myorelaxant. Several neurological side effects have been reported in association with TCC treatment including somnolence, confusion and seizure, the latter in a low percentage of patients. However, a major epileptological complication, such as status epilepticus, has never been previously reported in association with TCC treatment. In the present report, we described a case of acute refractory NCSE in the context of a TCC-induced acute toxic encephalopathy (ATE) in a woman without any previous neurological or physical comorbidities. Diagnosis of acute toxic NCSE was made according to Salzburg Criteria, considering the EEG features combined with the clinical improvement after i.v. benzodiazepine
and Death after intrathecal administration of daunomycin

In this report, after

However, MRI findings depend

treatment of lower back pain should initially involve the use

Neuropsychological assessment

According to our report, no specific brain MRI find-

and cogni-

Indeed, in the context of ATE,

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TABLE 1

Neuropsychological assessment

| Neuropsychological assessment                  | Score (equivalent score) |
|-----------------------------------------------|--------------------------|
| Mini-mental state examination (MMSE)          | 28                       |
| Digit span                                    |                          |
| • Forward                                     | 7 (4)                    |
| • Backward                                    | 2 (0)                    |
| Corsi block-tapping test                      |                          |
| • Forward                                     | 6 (4)                    |
| • Backward                                    | 5 (3)                    |
| Babcock story recall                          |                          |
| • Immediate recall                            | 4.7 (2)                  |
| • Delayed recall                              | 6.4 (3)                  |
| Free and cued selective reminding test        |                          |
| • IFR                                         | 24 (1)                   |
| • ITR                                         | 36/36                    |
| • DFR                                         | 8 (1)                    |
| • DTR                                         | 12/12                    |
| Trail making test (TMT)                       |                          |
| • Part A                                      | 24.72º (4)               |
| • Part B                                      | 84º (3)                  |
| Fluency                                       |                          |
| • Phonemic                                    | 45 (4)                   |
| • Semantic                                    | 49 (4)                   |
| Rey-Osterrieth figure                         |                          |
| • Copy                                        | 35 (4)                   |
| • Delayed                                     | 11 (0)                   |

Test scores were calculated with correction for age and education. Mini-
mental state examination (MMSE): a score of 24 or over is considered
normal. For each score, equivalent score is reported in brackets.
Equivalent score key: (4) over average; (2) and (3) normal score; (1) below
average; (0) severe deficit.

injection. We acknowledge that also ATE itself can be associated
with a similar EEG pattern. However, in ATE the administration
of antiseizure medications should not determine any clinical
improvement.

ATE reflects a global cerebral dysfunction of rapid onset and may
be associated with alterations in the level of consciousness. The caus-
ative agents include organic solvents or pharmaceutical compounds
which can diffusely affect brain function. According to the literature,
other cases of ATE associated with status epilepticus secondary to
inadvertent intrathecal injections include tranexamic acid
and bupivacaine. Death after intrathecal administration of daunomycin
has also been described.

Three basic principles of neurotoxicology are particularly relevant
to the diagnosis of toxic encephalopathy: (1) dose–response relation-
ship between toxic agents and neurological symptoms, (2) non-focal
or symmetrical neurological signs and (3) a strong temporal relation-
ship between exposure and symptom onset. In our report, all three
criteria were met. In particular, the close temporal relationship
between TCC injection and NCSE onset (as well as the exclusion of
any other condition at the basis of the clinical picture), and the pecu-
liar clinical picture (i.e., NCSE) associated with diffuse EEG abnor-
malities have supported the hypothesis of TCC-induced ATE. Even though
the TCC vial contained several excipients such as sodium chloride,
hydrochloric acid and water for injectable solutions, none of them
were associated with clinical onset of ATE or status epilepticus in
experimental or clinical settings.

Management of status epilepticus is based on a stepwise
approach. According to the International League Against Epilepsy, the
first line of treatment includes benzodiazepines (specifically intra-
muscular midazolam, intravenous lorazepam or intravenous diazepam),
which can be repeated up to two times. After a first attempt with ben-
zodiazepines, second-line therapy consists of the administration of
antiseizure drugs (e.g., levetiracetam, fosphenytoin, valproic acid). If
the second line of therapy fails to stop the seizures, treatment should
include repeating second-line therapy or proceeding to the adminis-
tration of anaesthetics (e.g., propofol, thiopental, midazolam, pento-
obarbital). In our patient a first administration of benzodiazepines was
performed; the latter was not repeated due to low blood oxygen
levels. Therefore, a second line approach was started with subsequent
poor response, hence a third line treatment was administered with a
complete electroclinical response.

Diagnosis of ATE is generally clinically driven even though neuro-
radiological findings may be useful. Indeed, in the context of ATE,
brain MRI often shows focal or diffuse white matter abnormalities as
well as basal ganglia involvement. However, MRI findings depend
on the specific toxic compound and a normal neuroradiological picture
can be found. According to our report, no specific brain MRI find-
ings were detected in the acute phase of TCC intoxication.

ATE sequela can include residual cognitive impairment (primarily
attention and information-processing impairment resulting in dysfunc-
tion in working memory) as well as focal neurological deficits. Previous
reports described persisting neurocognitive impairments in the con-
text of ATE caused by intravenous methadone injection, and cogni-
tive decline, parkinsonism, pyramidal signs and polyneuropathy after
long-term occupational solvent exposure (toluene, xylene, methyl-
ethylketone, resins, carbon disulfide, thinners). In this report, after
TCC exposure, our patient developed a long-lasting amnestic MCI.
Hence, TCC exposure may have impaired irreversibly the patient’s
cognitive performance.

4 | CONCLUSION

The present report describes a case of TCC-induced toxic encephalitis
associated with acute NCSE. Care should be taken in the management
of low back pain. In accordance with the European Medicines
Agency, treatment of lower back pain should initially involve the use
of non-steroidal anti-inflammatory drug (NSAID) medications such as
ibuprofen. If the patient cannot take NSAIDs, alternative medicines
such as codeine may help. Muscle relaxants such as TCC may be pre-
scribed by a general practitioner if the patient has painful muscle

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spasms. However, as described in our case report, TCC treatment can be associated with several life-threatening side effects. In line with this evidence, the European Medicines Agency's Committee on Human Medicinal Products (CHMP) has recommended that the authorized uses for thiocolchicoside-containing medicines delivered orally or by intramuscular injection should be restricted across the European Union (EU). Accordingly, intrathecal injection of TCC should be avoided.

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COMPETING INTERESTS
The authors declare no conflicts of interest.

CONTRIBUTORS
G.E. and F.D. contributed to the conception and design of the study. G.E., F.D. and S.C. wrote the manuscript. D.C. and M.R. performed the neuropsychological assessment. C.D. and M.C. interpreted MRI brain images. All authors contributed to manuscript revisions, read and approved the submitted version.

DATA AVAILABILITY STATEMENT
The data are available from the corresponding author upon reasonable request.

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