Drug-induced Creutzfeldt-Jakob disease-like syndrome: early CSF analysis as useful tool for differential diagnosis

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SUMMARY
We report the case of a 78-year-old man who showed a subacute onset of severe cognitive impairment, ataxia, tremor, stimulus sensitive myoclonus and hypophonia. Since a few weeks, he received a treatment with a combination of tricyclic antidepressants for mood disorder. The clinical picture mimicked Creutzfeldt-Jakob disease (CJD), but we could rule out this diagnosis by means of cerebrospinal fluid (CSF) analysis, which showed normal level of tau protein and Aβ1-42 being also negative for CSF 14-3-3 protein. A complete clinical recovery was observed after the discontinuation of antidepressants. So far, some cases of drug-induced CJD-like syndrome have been described. In our experience, early CSF analysis shows high diagnostic usefulness in order to exclude CJD.

BACKGROUND
Drug-induced Creutzfeldt-Jakob disease (CJD)-like syndrome is characterised by rapid cognitive deterioration, myoclonus and parkinsonian features, similar to what observed in CJD. In the last decades, some cases of drug-induced CJD-like syndrome have been described. With our case, we illustrate that physician suspecting CJD should be aware of the possibility of drug-induced neurotoxicity and should carry out early cerebrospinal fluid (CSF) analysis to confirm or exclude it.

CASE PRESENTATION
A 78-year-old man was admitted to our neurological clinic for a clinical picture of subacute, progressive cognitive impairment associated with tremor, gait disturbances, unsteadiness and slurred speech, started 3 weeks before. In the last few days, his clinical conditions rapidly deteriorated producing a significant impairment of functional abilities in daily living. He needed help for walking, due to the progressive ataxia with postural instability. Since 2 months, for a depressive disturbance, he was taking amitriptyline 60mg/day and clomipramine 75mg/day. His familial history was negative for neurological disease. Neurological examination revealed dysarthria and dysmetria, hypophonia, normal ocular movements, mixed (rest and action) tremor of the upper and lower limbs, fluctuant and stimulus sensitive myoclonus of the upper limbs and gait ataxia. He showed diffuse rigidity prevailing at the upper limbs, in absence of pyramidal signs. No visual hallucinations were reported by the patient and his relatives. Neuropsychological assessment was possible only bedside, due to postural instability and mental fatigue. Mini-Mental State Examination score was 26/30. Impaired scores were obtained in tests assessing verbal memory (Rey Auditory Verbal Learning Test) both in recall and recognition, executive functions assessed by means of Frontal Assessment Battery, phonemic and semantic fluency, visuospatial abilities evaluated by means of Clock-Draw Test. The patient appeared apathetic, also showing a marked psychomotor slowness.

INVESTIGATIONS
Brain MRI showed unspecific white matter lesions in both cerebral hemispheres associated to age-related cortical atrophy, in absence of enhancement after gadolinium, and diffusion-weighted sequences were normal, as well (figure 1). Basic CSF analysis (cell count, glucose and protein concentration) did not reveal pathological findings. CSF cytology and PCR for viruses were negative. CSF Aβ42/Aβ40 ratio, total tau and phosphorylated tau were in the normal range (0,110; 169pg/mL; 23pg/mL, respectively). CSF 14-3-3 protein was negative, as well. The electroencephalogram (EEG) revealed only unspecific slow abnormalities of the background electric activity, but it did not evidence pathological findings. Routine blood serum, infectious (HV, Treponema pallidum, Borrelia burgdorferi) and autoimmune screening (anti-nuclear antibodies, extractable nuclear antigens, anti-thyroid peroxidase antibodies, anti-glutamic acid decarboxylase antibodies, anti-transglutaminase antibodies) and paraneoplastic antibodies (classical onconeural antibodies and antibodies against neuronal surface/synaptic antigens) were negative. The patient underwent a total-body CT scan that was also negative for neoplastic lesions.
Differential Diagnosis

The diagnosis of CJD was ruled out by CSF, imaging and EEG findings. Central nervous system infectious, metabolic, autoimmune and paraneoplastic encephalitides were excluded as well. Other neurodegenerative forms of cognitive impairment and gait disturbances were not considered due to the subacute onset and the progressive course of the disturbances along a few weeks.

Outcome and Follow-Up

Marked clinical improvement occurred after the discontinuation of the tricyclic antidepressants. Myoclonus, dysarthria and gait difficulties disappeared in a few days. Cognitive status and mood significantly improved as shown by the neuropsychological examination repeated after 6 months.

Discussion

Sporadic CJD is a fatal and untreatable prion disease. Several conditions, potentially reversible, can mimic CJD.2 Drug toxicity, especially lithium toxicity, is considered among the differential diagnosis.8–10 So far, some cases of drug-induced CJD-like syndrome have been described, characterised by a rapid progressive cognitive impairment and often showing gait ataxia, myoclonic jerks and parkinsonian signs. Lithium, either alone10–12 or in combination with other medications12 such as nortriptyline,11 was the drug responsible for most of the cases. Only one case was related to high dosage of amitriptyline (150mg/day).11 In our case two tricyclic antidepressants, amitriptyline and clomipramine, at a medium dosage (60 mg/day and 75 mg/day, respectively), were implicated. CSF analysis represents a fundamental diagnostic tool in the management of rapid progressive dementia mimicking CJD.2 In another case of reversible lithium neurotoxicity mimicking CJD, CSF analysis did not reveal gross abnormalities.12 A positive 14-3-3 CSF assay is included in the proposed updated diagnostic criteria for probable CJD.13–15 It should be mentioned that a negative CSF 14-3-3 test might be compatible with variant CJD (vCJD) forms. Also, genetic, iatrogenic and rare subtypes of sporadic CJD can be negative for 14-3-3 immunoblot, but they can present elevated levels of tau protein (>800 pg/mL).16 Patients with vCJD often present psychiatric symptoms: CSF tau protein levels are useful in the differential diagnosis since patients with true psychiatric disorders (depression, psychosis) have normal values of CSF tau protein.17 Determination of tau protein levels in CSF is a useful marker for laboratory diagnosis.18 Some authors indicated the t-tau protein as the most sensitive and specific of the diagnostic markers for CJD.19 In particular, tau protein determination with a threshold of 1300pg/mL has a higher specificity than 14-3-3 (97% vs 92%) protein for CJD.20 CSF β1-42 can be reduced in patients with CJD, similar to what observed in Alzheimer’s disease.21,22 CSF analysis showed normal t-tau, p-tau and β1-42/β1-40 ratio in our patient, which could allow us to definitely rule out CJD.

Contributors

FPP: study concept and design, acquisition of data, analysis and interpretation of data. MDG: study concept and design, acquisition of data, analysis and interpretation of data. PC: study concept and design, acquisition of data, analysis and interpretation of data. LP: study concept and design, acquisition of data, analysis and interpretation of data, study supervision, critical revision of manuscript for intellectual content.

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Unusual presentation of more common disease/injury

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