Neurological Sciences (2019) 40:1073–1075
https://doi.org/10.1007/s10072-018-3646-1

LETTER TO THE EDITOR

A new neurobehavioral phenotype of familial Creutzfeldt–Jakob disease: impaired theory of mind

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Received: 31 August 2018 / Accepted: 12 November 2018 / Published online: 27 November 2018

Dear Editor-in-Chief,

Creutzfeldt–Jakob disease (CJD) is a neurodegenerative condition related to proteinaceous particles (prions) leading to neuron loss, astrocytic reactions, and spongiform changes. About 5–15% of cases are familial (fCJD), while up to 95% are sporadic and few cases are linked to iatrogenic transmission or bovine spongiform encephalopathy [1]. The phenotypes are heterogeneous between and within these groups. Common symptoms are dementia, ataxia, myoclonus, hallucinations, and insomnia. Dementia involving language, executive and visual functions has been associated with frontal, temporal, or parietal degeneration [2]. However, its fast clinical course usually prevents to characterize specific neurobehavioral phenotypes linked to defined CJD forms.

Theory of mind (ToM), a main aspect of social cognition, allows to represent and understand one's own and others' mental states [3]. The basal ganglia, cerebellum, amygdala, prefrontal medial and inferior cortex, orbital cortex, superior temporal sulcus, and temporoparietal junction cooperate within a complex cortical and subcortical neural circuit, supporting different ToM processes [4–6]. Given the distribution of brain degeneration, it is likely that CJD affects ToM. This study reports a yet un-described neurobehavioral profile of fCJD marked by early ToM impairment.

A 54-year-old right-handed patient (WO) with 13 years of schooling complained of behavior changes (irritability, anxiety, poor inhibitory control, insomnia, decreased appetite, fatigability, loss of interests, and social isolation) followed by later appearance of word-finding difficulty, poor motor balance, jerks, and mood depression. Two months after clinical onset, neurological examination revealed a playful uninhibited behavior alternated to apathy or impulsivity, irritability, fluctuating attention, anomia, and spontaneous arms' myoclonus. WO's father died after a brief neurological disorder characterized by fast cognitive and motor decline. Electroencephalogram recorded slow and spike waves on the left temporal region. Visual evoked potential showed an increased latency, while auditory and sensorial potentials were normal. Magnetic resonance revealed restricted diffusivity signal in the caudate nucleus bilaterally more severe on the left side and on the left temporal cortex. Positron emission tomography showed significant reduction of glucose metabolism in the left temporal lobe and caudate nucleus and mild reduction in the left occipital lobe (Fig. 1). The 14.3.3 protein was present, and TAU protein level was markedly increased in the cerebrospinal fluid. The prion protein (PRNP) gene analysis revealed an E200K mutation, confirming diagnosis of fCJD.

Neuropsychological assessment was performed 2 months after clinical onset (Table 1). WO was alert and oriented but showed highly variable performances across tests. The faux pas task (FPT) requires to recognize or to exclude the presence of a faux pas in 20 stories and to comprehend the epistemic and affective mental states of the stories' characters. It is a developmentally advanced task able to detect subtle ToM impairments in adult subjects [3]. A test using photographs of actors' faces, each displaying a basic emotion, assessed emotion recognition (ER) [5]. General and specific cognitive functions were also evaluated [4, 5]. Awareness of disease was preserved. Working memory, episodic memory, constructive

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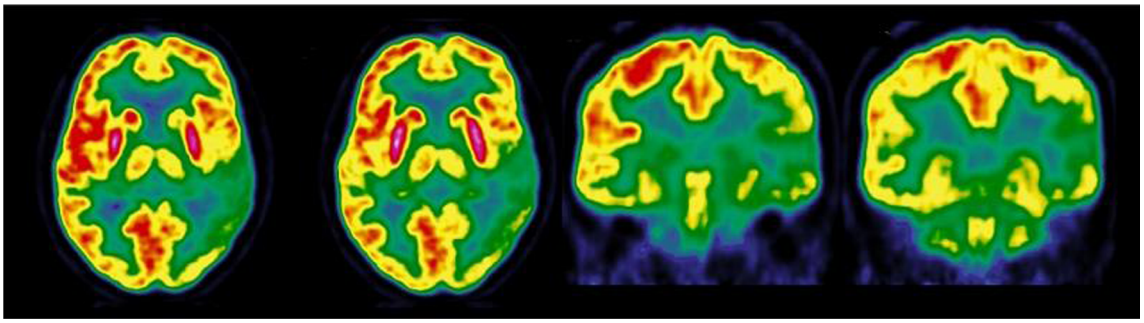

Fig. 1 Positron emission tomography of the brain. The transverse and coronal images reveal a significant reduction of glucose metabolism in the left temporal lobe and caudate nucleus and a mild reduction in the left occipital lobe

praxis, the graphic representation and organization of visuospatial items, the speed of visuomotor coordination, abstract reasoning, and overall cognitive functioning were normal. The FPT and ER scores were lower in comparison with healthy subjects and very similar to those reported by neurological patients [4, 5]. ToM was marked by an altered comprehension of false beliefs, intentions, and affective mental states, although the recognition of real faux pas and the exclusion of non-existent mental states were normal or mildly impaired. Selective and divided attention were at the lowest normal range. Naming of line drawings, word fluency on phonemic or semantic cues, and executive functions were impaired in comparison with the corresponding normative values [4, 5]. At the Aachener Aphasie test, spontaneous speech was communicative but grammatically incorrect, with short sentences, grammatical alterations (e.g., incorrect morphemes and articles), anomia, and semantic and phonemic paraphasias; oral and written comprehension and repetition were mildly to moderately impaired, while reading and writing were normal. Two months after diagnosis, the clinical picture was unchanged; no instrumental or laboratory follow-up was done. As a whole, the cognitive profile was marked by impaired ToM, ER, and executive functions and mild non-fluent aphasia, pointing to a prominent left hemisphere dysfunction.

The E200K PRNP mutation, the most common genetic alteration of fCJD, is associated with various clinical phenotypes that always include fast cognitive decline, behavior

Table 1 Neuropsychological findings

Neuropsychological tests	Raw scores	Equivalent/cut-off scores[a]
Attentive matrices	38	1
Trail making test A	62	2
Trail making test B	197	1
Digit span	5	3
Corsi block span	4	2
Rey's complex figure delayed recall	10.5	2
Word fluency on semantic cues	9	0
Word fluency on phonemic cues	7	0
Aachener Aphasie test		
Token test	36	Moderate impairment
Repetition	109	Moderate impairment
Writing	83	Minimum impairment
Naming	73	Moderate impairment
Comprehension	106	Mild impairment
Raven's colored progressive matrices	34	4
Frontal assessment battery	11	Cut-off = 16.5
Rey's complex figure copying	33	4
Faux pas task	8/13	Cut-off = 11
Emotion recognition test	30/40	
Mini mental state examination	28	Cut-off = 24

[a] The equivalent scores correspond to five categories of age- and schooling-adjusted scores of a normative healthy population where 0, impaired performance; 1, borderline performance; and 2 to 4, average to high-level performance

changes, cerebellar or visual signs, myoclonus, and sensory and cranial nerve defects. Atypical presentations include auditory agnosia, pseudobulbar palsy, and limb dystonia. Previous studies reported homogeneous cognitive profiles, characterized by aphasia or executive deficits [2]. This is the first study analyzing ToM and ER at the clinical onset in fCDJ. Impaired ToM and ER, associated with congruent behavior changes, may relate to degeneration of the caudate nucleus [6], although the left temporal lobe dysfunction also affects ToM [5]. Patients with temporal lobe epilepsy [5], cerebellar atrophy [4], Parkinson's disease, or Huntington's disease (HD) [6] exhibit poor recognition of facial emotions and ToM. ToM changes can precede motor onset in basal ganglia disorders, while impaired social cognition is a known marker of HD onset and progression, supporting the attribution of affective ToM to the basal ganglia [6]. Impaired ToM and ER, associated with congruent behavior changes, highlight a previously un-described neurobehavioral phenotype of fCJD, which expands the clinical markers of CJD degeneration.

Compliance with ethical standards

Conflict of interests The authors declare that they have no competing interests.

Ethical publication statement We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. The study has been performed in accordance with the 1964 Declaration of Helsinki and its later amendments. The patient gave informed consent to the clinical and instrumental examinations.

References

1. Heider E, Wali W, Raja S et al (2013) Creutzfeldt Jakob disease. J Coll Physicians Surg Pak 23:295–297
2. Caine D, Tinelli RJ, Hyare H, de Vita E, Lowe J, Lukic A, Thompson A, Porter MC, Cipolotti L, Rudge P, Collinge J, Mead S (2015) The cognitive profile of prion disease: a prospective clinical and imaging study. Ann Clin Transl Neurol 2:548–558. https://doi.org/10.1002/acn3.195
3. Stone VE, Baron-Cohen S, Knight RT (1998) Frontal lobe contributions to theory of mind. J Cogn Neurosci 10:640–656
4. Giovagnoli AR, Parente A, Villani F, Franceschetti S, Spreafico R (2013) Theory of mind and epilepsy: what clinical implications? Epilepsia 54:1639–1646. https://doi.org/10.1111/epi.12255
5. Parente A, Manfredi V, Tarallo A, Salsano E, Erbetta A, Pareyson D, Giovagnoli AR (2013) Selective theory of mind impairment and cerebellar atrophy: a case report. J Neurol 260:2166–2169. https://doi.org/10.1007/s00415-013-6985-0
6. Bodden ME, Dodel R, Kalbe E (2010) Theory of mind in Parkinson's disease and related basal ganglia disorders: a systematic review. Mov Disord 25:13–27. https://doi.org/10.1002/mds.22818