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BRIEF COMMUNICATION

Cognitive dysfunction, social behavior disorder, cerebellar ataxia, and atypical brain FDG-PET presentation in spinocerebellar ataxia 17: a case report

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Abstract

Background Spinocerebellar ataxia 17 (SCA17) is a rare autosomal dominant form of inherited ataxia, caused by heterozygous trinucleotide repeat expansions encoding glutamine in the TATA box-binding protein (TBP) gene.

Case description We describe the clinical history, neuropsychological, and neuroimaging findings of a 42-year-old patient who presented for medical attention showing prevalent behavioral and cognitive problems along with progressively worsening gait disturbances. The patient's family history indicated the presence of SCA17 in the maternal lineage. Genetic analysis confirmed a heterozygous 52-CAG pathological expansion repeat in TBP (normal interval, 25–40 CAG. Brain 18-fluorodeoxyglucose positron emission tomography (FDG-PET) showed bilateral hypometabolism in the sensorimotor cortex, with a slight predominance on the right, as well as in the striatal nuclei and thalamic hypermetabolism, a finding similar to what is observed in Huntington's disease. The patient also underwent neuropsychological evaluation, which revealed mild cognitive impairment and difficulties in social interaction and understanding other's emotions (Faux Pas Test and Reading the Mind in the Eyes Test).

Conclusion Our report emphasizes the importance of considering SCA17 as a possible diagnosis in patients with a prevalent progressive cognitive and behavioral disorders, even with a pattern of FDG-PET hypometabolism not primarily indicative of this disease.

Keywords Spinocerebellar ataxias · Hereditary ataxias · Positron emission tomography · Huntington disease · Social behavior disorders · Mentalization

Introduction

Spinocerebellar ataxia 17 (SCA17) is a rare autosomal dominant form of inherited ataxia. The disease is caused by heterozygous expansion of a trinucleotide repeat encoding glutamine (CAG or CAA) in the TATA box-binding protein gene (TBP), on chromosome 6q. Typical manifestations are ataxia and psychiatric abnormalities, followed by parkinsonism, chorea, dementia, and pyramidal signs. For its clinical features, SCA17 has also been termed Huntington's disease-like 4.

However, SCA17 is a complex disease with extensive phenotypic variability and a complex genetic pattern. The age at onset ranges from 3 to 60 years. Clinical features and penetrance correlate with the length of the polyglutamine expansion. Anticipation is rare, and it is usually related to

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the lack of a CAA CAG CAA element within the expanded CAG repeat. Full penetrance is typical of individuals showing a CAG/CAA repeat size of TBP ≥ 47, whereas incomplete penetrance has been described for intermediate repeat sizes of 41–46 [1, 2]. Recently it has been demonstrated that intermediate repeat sizes of TBP alleles cause the disease only if a STUB1 variant is present [3, 4]. Indeed, recent studies demonstrated that only in fully penetrant CAG expansion (repeat size of TBP > 49) the length of the polyglutamine expansion correlates with the age of onset [5].

Case description

We describe the case of a 42-year-old man who had been complaining of a behavioral disorder characterized by social isolation, apathy, irritability, and verbal aggression for about 3 years. These symptoms had been subsequently accompanied by progressively worsening gait disorders, cognitive impairment, and mild dysphagia. The patient's family history was positive for genetically confirmed SCA17 on the maternal lineage, and no anticipation was referred.

The neurological examination revealed a gait and upper limb ataxia mildly prevailing on the right side, cerebellar dysarthria, difficulties in fine movements of the hands, reduced lower limb proprioception, and widely increased deep tendon reflexes. Involuntary movements or parkinsonism were not observed. Remote pathological history and routine blood tests showed no major findings.

Frontal, hippocampal, cerebellar, brainstem atrophy, and bilateral pale nuclei hypointensity were noted on gradient echoT2-weighted sequences on magnetic resonance imaging.

A lumbar puncture was performed, and the cerebrospinal fluid analysis revealed normal protein concentration and cell count. Levels of amyloid-beta 1–42 and 1–40, phosphorylated-tau at 181, and total tau resulted within the normal range. No antibodies against the central nervous system were identified on cerebrospinal fluid.

The genetic analysis confirmed the clinical diagnosis, revealing a heterozygous pathological expansion of CAG triplets in TBP, with 52 repetitions (normal interval, 25–40). Brain 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) showed bilateral hypometabolism of the sensorimotor cortex, with a slight predominance on the right, and of striatal nuclei; interestingly, thalamic hypermetabolism was also demonstrated. No significant hypometabolism or distribution asymmetries were evident in the cerebellum (Fig. 1).

Neuropsychological evaluation detected a mild to moderate cognitive impairment regarding executive and visuospatial functions, attention, linguistic, and praxis abilities (full neuropsychological evaluation can be found in supplementary materials). Two scales of assessment for mind theory skills were given: Faux Pas Test and Reading The Mind in the Eyes. The Faux Pas Test is a measure of empathic comprehension skills, which investigate the ability to recognize Faux Pas and to evaluate empathic abilities [6]. The patient's score was 26/60: the ability to recognize errors and comment on them was preserved, while the ability to empathize was lacking. The test Reading the Mind in the Eyes investigates the ability to infer complex mental states by means of information coming from the face. The patient showed a score of 17/36; his mentalization capacity could be interpreted as falling at the lower limit of the norm, based on the reference normative data for the Italian population [7]. Activities of daily living were retained, while instrumental activities of daily living were reduced (4/8). At the 6-month visit, the clinical picture remained stable. No benefits were reported from sertraline therapy.

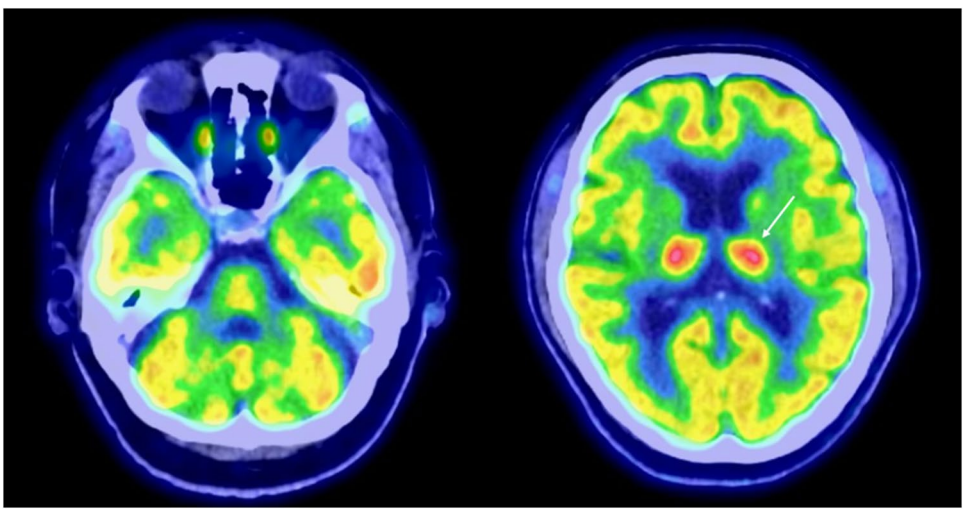

Fig. 1 Axial brain FDG-PET sections showing bilateral hypometabolism of the sensorimotor cortex and of striatal nuclei, with thalamic hypermetabolism (white arrow). No significant hypometabolism was evident in the cerebellum

Discussion

Our report provides detailed clinical and neuroimaging findings in a SCA17 case.

According to the fact that SCA17 may represent a phenocopy of Huntington disease (HD) [8], the PET's findings in our case are very similar to the ones which can be found in HD. To the best of our knowledge, this peculiar PET's presentation was never previously described in a case of SCA17; previous descriptions only reported hypometabolism of the cerebral cortex, cerebellum, and basal ganglia, without mentioning the possibility of thalamic hypermetabolism [8]. Such findings should not lead to the exclusion of SCA17 as a possible diagnosis.

In addition, our case description quantifies and highlights the importance of cognitive, psychological, and social functioning-related aspects in this rare disorder, emphasizing its complexity and phenotypic pleiotropism.

An important behavioral impairment was already described as a paramount feature of SCA17, which can move the clinician toward a wrong diagnosis of other types of presenile dementia, like frontotemporal dementia and the already cited Huntington disease [9, 10]. We provide an in-depth description of the patient's neuropsychological picture, and, to the best of our knowledge, for the first time in SCA17 patients, tests were performed to measure levels of theory of mind reasoning.

Our comprehensive neuropsychological evaluation revealed mild to moderate cognitive impairment across various domains, including executive and visuospatial functions, attention, linguistic, and praxis abilities. In the Faux Pas Test, the patient demonstrated preserved error recognition but lacked empathic abilities. Reading the Mind in the Eyes revealed a mentalization capacity at the lower limit of the norm. Our study fills a crucial gap by providing detailed neuropsychological profiles of SCA17 patients, contrasting with previous literature that lacks comprehensive cognitive assessments [11–13]. While earlier research discusses cognitive involvement broadly, our study highlights specific cognitive domains affected in SCA17. Through extensive evaluations covering executive functions, attention, language, and visuospatial abilities, we show the multifaceted cognitive impairment in SCA17. Investigating the theory of mind abilities in patients with neurodegenerative disorders is crucial for understanding their social cognition and interpersonal functioning and clarifying differential diagnosis. Formica et al. [14] highlighted that theory of mind (TOM) plays a crucial role in the differential diagnosis of dementias and the management of patients. In neurodegenerative diseases like Alzheimer's disease and frontotemporal dementia, TOM deficits manifest differently, aiding in distinguishing between these conditions. Understanding TOM's role enhances diagnostic accuracy and enables tailored interventions, addressing patients' specific needs and enhancing their quality of life amidst neurodegenerative challenges. Our findings emphasize the need for comprehensive cognitive assessment in SCA17 diagnosis and management, contributing to tailored interventions and support strategies for affected individuals.

Our report provides another evidence of the role of the cerebellum in social cognition. In the last decades, clinical and pre-clinical research have unveiled the relationship between the cerebellum and cognitive and behavioral functions [15]. This role of the cerebellum can be explained by the connection with the cerebral cortex, especially the frontal cortex, due to cortico-ponto-cerebello-thalamo-cortical loops. Since the seminal work of Schmahmann, who introduced the concepts of dysmetria of thoughts and cerebellar cognitive affective syndrome as possible manifestation of cerebellar lesions, several other studies have highlighted that hereditary ataxias can express themselves with behavioral and cognitive symptoms [16]. Nevertheless, degeneration in hereditary ataxias, like SCAs, is not usually confined to the cerebellum, but it also interests several other brain regions. It is remarkable that cognitive impairment can be evident even if the cerebellum is the only structure affected, but it is more pronounced when even cerebral cortex and basal ganglia are involved, like in SCA17 [17]. The literature is poor of studies analyzing social faculties of patients suffering of spinocerebellar ataxias. In future perspectives, it is advisable to better explore social and affective disorders in patients with SCA17 and other rare types of genetic ataxias.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10072-024-07453-4.

Author contribution All the authors contributed to the study conception and design. Material preparation and data collection were performed by AG, AC, FR, AM, FF, and EP. Neuropsychological examination was performed by AC, genetic analysis by AB, nuclear medicine imaging by MZ e AL. The first draft of the manuscript was written by AG and AC, and all the authors edited the subsequent versions. The final review was done by IR, ACB ER, and SB. All the authors read and approved the final manuscript.

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Data availability Further clinical and genetic data will be available upon request from any qualified investigator.

Declarations

Ethical approval Ethical approval was obtained from the local Committee of the Città della Salute e della Scienza di Torino (protocol 0114576). The patient has consented to participate to the study and to the submission of the case report to the journal.

Conflict of interest The authors declare no competing interests.

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