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LETTER TO THE EDITOR

A case of hemichorea/hemiballismus in a patient with Alzheimer's disease and history of Sydenham's chorea: the return of an old acquaintance?

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Dear Editor,

Sydenham's chorea (SC) is a post-infectious syndrome that occurs in people who have streptococcal pharyngeal infection and rheumatic fever and is caused by the autoimmune response against components of the basal ganglia. It is characterized by the onset of choreiform movements that usually appear up to six months after infection [1]. In addition to motor problems, there is classically emotional lability, anxiety, attention deficit [1]. In most cases, SC typically improves in a few months, but patients can be affected for years by persistence and recurrence of both neurological and neuropsychiatric symptoms [1]. Chorea recurrences affect 15–30% of patients within 2–3 and up to 10 years after onset; nevertheless, only a few cases of later recurrence have been reported [2]. Here, we present the case of a Caucasian woman in her 70s experiencing relapse of SC concurrent with the onset of Alzheimer's disease (AD). She was referred to the Centre for Alzheimer's Disease and Adult Cognitive Disorders of Careggi Hospital in Florence for a 4-year history of memory deficits and mood deflections. At the time of the first evaluation, the patient was completely autonomous and was referred to regular sleep patterns. She denied any familiarity with neurological disorders. She reported a medical history of blood hypertension, hypercholesterolemia, pacemaker for sick sinus syndrome, and Rheumatic Fever (RF), which presented with SC at 9 years of age. Neither the patient nor her relatives were able to confirm whether RF was treated with antibiotics. She was taking drugs for blood hypertension, hypercholesterolemia, and an SSRI (escitalopram) that was prescribed by her general practitioner without efficacy. At the first neurological examination, the patient presented as lucid, collaborative, with fluent, informative, well-articulated, and communicative speech. The remaining neurological examination was unremarkable. An extended neuropsychological evaluation revealed moderate multi-domain cognitive decline (MMSE score of 21/30), mild disinhibition, and lack of insight. Brain computed tomography (CT) showed diffuse cortical atrophy, cerebral ventricular dilatation, and chronic vascular leukoencephalopathy. At the three-month follow-up visit, her son reported a progression of cognitive and behavioral symptoms, including social conduct abnormalities, restlessness, verbal aggressivity, obsessive thinking, and degradation in autonomy. Neurological evaluation showed involuntary hemicoreic/hemiballistic movements in the left limbs and facial grimacing (videos in the supplementary materials: Video 1: Alternating movements 1; Video 2: Alternating movements 2; Video 3: Gait). Spatial and temporal disorientation and logorrheic speech were also evident. Hypertonia, bradykinesia, or tremors were not observed. The patient was admitted to the Neurology Unit of our hospital, where all possible causes of acute/subacute hemichorea/hemiballismus were ruled out (Table 1). In particular, no clinical findings suggesting systemic autoimmune or toxico-metabolic

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Table 1 Possible causes of acute/subacute hemichorea/hemiballismus

Possible causes	Cognitive decline/ behavioral alterations	Clinics and/or assessment required for the diagnosis	Results in our patient
Huntington's disease	Yes	Huntingtin gene analysis	Negative
CBS due to AD / CBD	Yes	Clinical criteria (Armstrong et al. 2013). Confirmed by biopsy or autopsy	Excluded by hypermetabolism of basal ganglia. Autopsy not performed
Chorea-acanthocytosis or McLeod Syndrome	Yes	Blood test, EEG, brain imaging, assessment for systemic involvement, genetic testing	Absent acanthocytes, normal creatine kinase. No systemic involvement. EEG and CT scan not supportive
Wilson's disease	Yes	Blood ceruloplasmin, 24-h urinary copper excretion, serum free copper, hepatic copper, liver biopsy, Kayser–Fleischer rings, genetic testing for ATP7B mutations	Late age onset, negative ceruloplasmin, no systemic involvement, no liver failure
Ischemic/hemorrhagic brain lesion	Variably	Lesion of basal ganglia at brain imaging	No consistent lesions at brain CT scan
CNS infections	Variably	Neuroimaging. CSF analysis. Blood culture	Negative CT scan, CSF analysis and blood cultures
Prion disease	Yes	Brain MRI features, indicative EEG, 14–3-3, RTQuIC sensitive detection of PrP, genetic testing	No suggestive EEG features, negative 14–3-3 and RTQuIC
Paraneoplastic syndromes and autoimmune encephalitis	Yes	Subacute onset, CSF pleocytosis, MRI and EEG findings involving temporal lobes. Antibodies in CSF and blood	CSF and EEG features not supportive. Negative antibodies
Systemic autoimmune disease (LES, scleroderma, rheumatoid arthritis)	Variably	Clinical criteria, positive auto-antibodies	Not met clinical criteria, negative antibodies
Toxico-metabolic and nutritional disorders	Yes	Blood tests, gene analysis, drugs	Negative
Acute Sydenham's chorea	Yes	Testing for GAS infection	Negative

CBS, Corticobasal syndrome; *CBD*, Corticobasal degeneration; *CSF*, cerebrospinal fluid; *PrP*, Prion protein; *GAS*, group A streptococcus; *MRI*, Magnetic resonance imaging

diseases associated with movement disorders [3] were observed or reported. EEG examination showed bilateral slow and widespread non-specific abnormalities. A lumbar puncture was performed, and chemical and physical examination of cerebrospinal fluid was normal, excluding autoimmune encephalitis as no signs of neuroinflammation were evident. Moreover, a panel of antibodies more frequently involved in the onset of autoimmune encephalitis syndromes associated with hyperkinetic disorders (NMDAR IgG, LGI1 IgG, CASPR2 IgG, GABA B1/2-R IgG, GLUR1/2 IgG) was negative [4].

CSF AD biomarker analysis showed reduction of $A\beta_{42}$ (312 pg/ml, normal value [n.v.] > 600 pg/ml), increased total tau (695 pg/ml, n.v. < 400 pg/ml), and phosphorylated tau (84 pg/ml, n.v. < 61 pg/ml). A [18]F-fluorodeoxyglucose-PET brain scan showed bilateral and asymmetric (clearer in the right side rather than the left) temporoparietal hypometabolism and basal ganglia bilateral hypermetabolism (Fig. 1). These results were consistent with AD, while the basal ganglia hypermetabolism is common in SC[9]. Therefore, we proposed a diagnosis of late recurrence of SC in a patient with AD. Therapy with tetrabenazine (25 mg three times a day) was initiated, resulting in a significant reduction in involuntary movements. Additionally, low-dose quetiapine (25 mg daily) significantly reduced behavioral symptoms. At the follow-up visit after six months, the patient showed a complete resolution of the involuntary movements but exhibited progression of cognitive and functional decline typical of AD.

We speculated that neurodegeneration due to AD allowed permanent damage caused by post-streptococcal syndrome to manifest after a long period of remaining clinically silent. Indeed, a previous study revealed that persistent alterations of the basal ganglia are found in 20% of patients with SC one year after the first episode, and predict a greater number of recurrences. Typical MRI findings have also been reported in patients with recurrence of SC, including focal areas of T2 hypersignal in the caudate nucleus, globus pallidum, putamen, and white matter, corresponding to the contralateral side in cases of hemichorea [5]. The asymmetrical presentation of the movement disorder might mirror the asymmetric presentation of AD, with greater hypometabolism in the right temporoparietal regions of our patient (contralateral to limbs involved by hemichorea).

A similar case has been described by Harrison et al. [6]. In this case, the authors attributed movement disorder recurrence to neuronal loss associated with aging. They also reported that, in contrast to cases of acute or early recurrences of SC, their case was serum anti-basal ganglia antibodies (ABGA) negative, suggesting that late recurrences might be a consequence of dopamine hypersensitivity due to structural alterations in the basal nuclei more than a reactivation of the autoimmune response. Persistent damage following SC has also been observed in the dorsolateral prefrontal-striatal circuit and anterior cingulate loop [7], maybe contributing to the cognitive and behavioural disturbances in our patients. Similarly, psychiatric symptoms (anxiety and obsessive–compulsive disorder) were also reported in cases of late recurrence of SC [5]. Symptomatic treatment for chorea is based on a low-dose, high-potency dopamine 2 receptor-blocking agent [8]. In moderate to severe cases, immunosuppression with corticosteroids may be considered to shorten the duration of symptoms [8], and in severe cases, intravenous immunoglobulin or plasmapheresis has also been used [8]. In this case, tetrabenazine was effective in controlling involuntary movements.

This case report has two main limitations. First, we did not conduct an ABGA analysis of our patient. Second, we were unable to confirm our diagnostic suspicion through a brain anatomopathological examination but, we addressed our hypothesis of AD by investigating CSF biomarkers and [18]F-fluorodeoxyglucose-PET imaging. However, to the best of our knowledge, this is the first report of a case of AD

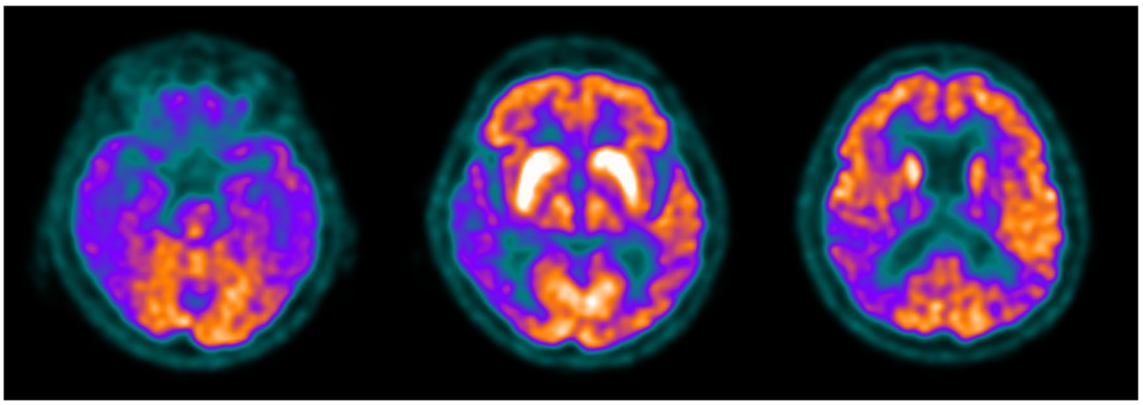

Fig. 1 [18]F-FDG-PET brain scan showing bilateral and asymmetric (more evident in the right side rather than the left) temporoparietal hypometabolism and basal ganglia bilateral hypermetabolism

presenting with symptoms suggestive of SC recurrence. If confirmed by further reports, this case may encourage clinicians to factor in a history of Sydenham's chorea when evaluating elderly patients presenting with hyperkinetic movement disorders. Furthermore, it may stimulate research into the potential links between AD and changes in brain structures affected by previous neurological or systemic conditions.

Abbreviations *SC*: Sydenham's chorea; *AD*: Alzheimer's disease; *RF*: Rheumatic fever; *CT*: Computed Tomography; *EEG*: Electroencephalogram; *CSF*: Cerebrospinal Fluid; *PET*: Positron Emission Tomography; *MMSE*: Mini-Mental State Examination; *SSRI*: Selective Serotonin Reuptake Inhibitor; *[18]F-FDG-PET*: [18]Fluorodeoxyglucose-Positron Emission Tomography; *CBS*: Corticobasal Syndrome; *ABGA*: Anti-Basal Ganglia Antibodies

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Data Availability The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Declarations

Conflict of Interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethical approval and Informed consent This study comply with the specific requirements of our institution about case report. Informed consent was obtained from the caregiver of the patient included in the case report. The caregiver has been informed about the purpose of the report and has provided written consent for the patient's clinical information and video recordings to be used for research and publication purposes. Consent for the inclusion of the video in the paper has also been granted by the caregiver.

Ethical standards statements This case report has been conducted in accordance with the ethical standards of the institution and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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