

Pathological gambling associated with CADASIL: an unusual manifestation

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Dear Editor,

This paper details a report concerning a case of PG associated with Cerebral Autosomal Dominant Arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).

CADASIL is an inherited small artery disease caused by mutations of the NOTCH-3 gene on chromosome 19 [1]. Usually, the first manifestations are attacks of migraine with aura, observed in 20–30 % of patients. Ischemic diseases, the most common clinical manifestations, are reported in 60–80 % of patients, generally during the fourth or fifth decade. Neuropsychiatric manifestations include mood disturbances and various degree of cognitive impairment, observed at all stages of the disorder. Psychiatric symptoms, mainly episodes of mood disturbances, are reported in 10–20 % of patients [2]. Pathological gambling (PG) is as a maladaptive and recurrent pattern of gambling behaviours that persists despite substantial negative consequences for the individual, his/her work and his/her family. Gambling disorders (referred to as pathological gambling in the DSM-IV) have been recently reclassified in the 5th DSM edition under the category of “Addictions and Related Disorders” because of similarities to substance use disorder (SUD) (i.e. genetic predisposition, treatment

response, clinical characteristics, cognitive deficits and underlying neurobiological mechanisms) [3]. A 39-year-old married male, unemployed and genetically diagnosed with CADASIL, carrying a heterogeneous mutation (R90C in the exon 3) of the NOTCH-3 on chromosome 19 p13.2-13.1 [1], was hospitalized to our neurological outpatient clinic for an episode of transient confusion. His family history revealed that his mother, suffering from CADASIL, died at age of 76 years after a stroke. Our patient had also a history of frequent attacks of migraine without aura since the age of 20 years. Furthermore, he and his relatives denied depressive episodes or previous diagnosis of mood disorder, and he did not display any sleep or eating disorders at the time of the visit. About 6 months before, he started to gamble every day, mainly football betting, slot machines and national lottery, cumulating about 40.000 euros in debts due to gambling. His wife reported that he had become excessively talkative, impulsive and verbally aggressive. During the hospitalization, his labile confusion completely resolved in a few days. Magnetic Resonance Imaging (MRI) of the brain revealed severe leukoencephalopathy with confluent and discrete, fairly symmetric T2 hyperintense foci in the deep and subcortical white matter of the cerebral hemispheres. Similar foci were present in the brainstem, thalami, basal ganglia and the subcortical white matter of anterior temporal lobes (Fig. 1). He had begun to impulse buy multiple items also make many unnecessary purchases for him or his family. When his mental condition was assessed, he showed no confirmation of delusions or hallucinations, but he did have labile moods, poor impulse control, and made grandiose plans. He demonstrated no insight into the changes in his personality and behaviour. Due to a suspected gambling disorder, neuropsychological testing was performed by a clinical psychologist. To evaluate his comprehensive

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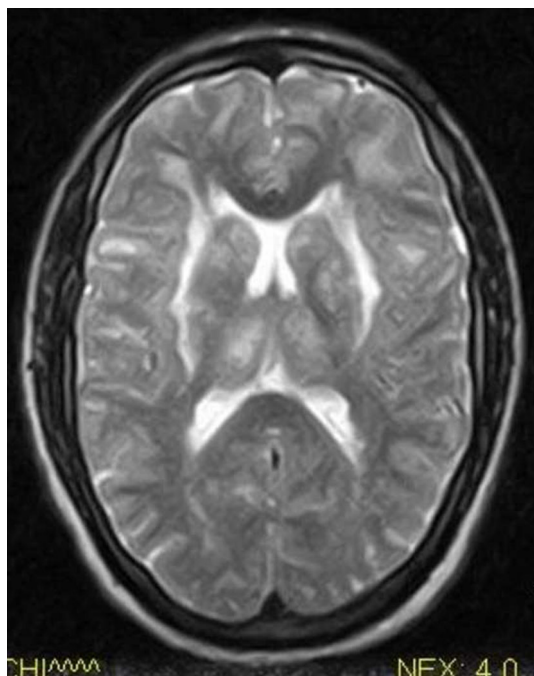


Fig. 1 MRI demonstration of confluent white matter hyperintensities on T2-WI

cognitive function, we performed the following tests: Mini-Mental State Examination (MMSE), Alzheimer’s Disease Assessment Scale, cognitive subscale (ADAS-Cog) and MMPI-II. Besides, we administered the South Oaks Gambling Screen (SOGS) [4] to assess gambling severity. Depressive mood state was assessed using the Beck Depression Inventory (BDI). MMSE and ADAS-Cog total scores were within normal range. The results of the MMPIII showed that scales 1 and 9 had higher scores. The assignment of a greater score to SOGS scale (=10) revealed the presence of a serious problem of pathological gambling. Finally, BDI scores showed no clinical relevance of depression (=14). The results of the neurological examination showed no abnormalities and routine laboratory tests including VDRL, HIV antibodies and thyroid function were also unremarkable apart from hyperlipidemia. To our knowledge, this is the first case of gambling described in a patient with CADASIL. Psychiatric disorders in patients with CADASIL are frequently reported to occur in the course of the disease [2] and are often the first recorded symptoms because the affected patients will first be admitted to a psychiatric clinic. A recent review article has highlighted that personality and behavioural disorders, such as irritability and hostility, were reported in only seven cases of a previous 454-patient cohort and that bipolar disorder was documented in nine cases of a 451-patient series [2]. However, these studies were limited by the fact that clinical manifestation was not defined by

psychiatric specialist. Most often, psychiatric disorders are observed in patients after diagnosis and a history of ischemic symptoms with signal abnormalities at MRI analysis. The location of ischemic lesions in basal ganglia and the frontal location of white matter lesions may play a key role in the occurrence of such mood disturbances in CADASIL patients [5]. In a previous study, Cognat et al. reported the case of a patient showed from PG—like behaviour subsequent a stroke involving subcortical structures [6]. Neurobehavioural and cognitive changes only occur when specific sub-cortical nuclei or portions of these nuclei are affected [7]. The exact mechanism of PG in our patient remains unknown. The main hypothesis is that accumulation of sub-cortical lesions may damage in particular the striato-cortical circuits linking basal ganglia to orbitofrontal areas. Lesion and experimental studies have demonstrated that the dorsal caudate is part of the anatomical and functional cortical-sub-cortical circuits critical for executive functions [8], and that damage to the caudate nucleus is associated with a “dorsolateral prefrontal like” syndrome [5]. While the vast majority of pathological gamblers do not have neurological comorbidities, PG has been reported in the field of behavioural neurology in patients with orbital–medial PFC lesions [9] and as a consequence of excessive dopaminergic stimulation, presumably resulting from an over-stimulation of the meso-cortical limbic dopaminergic pathway that may affect the functioning of the ventral PFC-ventral striatum circuit [10]. CADASIL is likely to be underdiagnosed disease, particularly in psychiatric patients. It is therefore important to highlight CADASIL to psychiatrists as a potential differential diagnosis. In conclusion, we suggest that in PG patients with different clinical features such as positive family history of stroke or psychiatric disorders and detection of white matter MRI abnormalities, it is appropriate to investigate CADASIL diagnosis. Further studies are needed to better understand the exact impact of cerebral tissue lesions and PG symptoms in CADASIL patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from the patients.

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