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Letter to the Editor

Cerebral microbleeds: A new presenting feature of chromosome 22q11.2 deletion syndrome

Abbreviations:
2q11.2DS
Topic:
22q11.2 deletion syndrome
CNS
Topic:
central nervous system
CMB
Topic:
cerebral microbleeds
Array CGH
Topic:
array - comparative genomic hybridization
EEG
Topic:
electroencephalography
CT
Topic:
computed tomography
MRI
Topic:
magnetic resonance imaging
FFE
Topic:
fast-field-echo
SWI
Topic:
susceptibility-weighted imaging
APOE
Topic:
apolipoprotein E
APP
Topic:
amyloid precursor protein
PFA-100
Topic:
platelet function assay
CAA
Topic:
cerebral amyloid angiopathy

Keywords:
Cerebral microbleeds
22q11.2 deletion syndrome
Platelet dysfunction

Dear Editor,

22q11.2 deletion syndrome (22q11.2DS) is a contiguous gene microdeletion syndrome that affects up to 1 in 2000 live births [1]. The commonly 22q11.2DS deleted region contains over 35 genes. >70% of the patients display congenital heart abnormalities, immune system deficiencies, palatal defects, structural renal anomalies and parathyroid hypoplasia. Structural central nervous system (CNS) abnormalities include spina bifida, microcephaly and reduced development of the grey matter [2]. 22q11.2DS patients also show behavioral disturbances, impaired cognitive development and seizures that can be triggered by cortical dysgenesis or by hypocalcaemia in hypoparathyroidism [3].

We describe a 36-year-old woman, admitted to our neurological unit because of episodes of brief loss of consciousness associated with motor arrest and brief postictal confusion. The patient had experienced the first episodes 4 years earlier. The loss of consciousness was sometimes accompanied by tonic-clonic movements. Her past medical history was remarkable for tetralogy of Fallot, surgically treated when she was 6 years old. At the age of 30, the patient developed a sustained depressed mood, treated with paroxetine for 2 years.

Neurological examination revealed increased muscle stretch reflexes, moderate dysdiadochokinesia and slight difficulty in the tandem walking test. Neuropsychological evaluation showed a mild cognitive impairment. EEG showed asymmetric generalised bursts of spike waves and polymorphic theta activity on the left frontotemporal regions. We investigated whether epileptiform activity was related to hypocalcaemia, but calcaemia (9.2 mg/dL, reference [8].1–10.4), phosphoraemia (3.1 mg/dL, reference [2].8–5.2) and parathyroid hormone level (28.4 ng/L, reference 13.0–64.0) were normal. Brain Magnetic Resonance Imaging (MRI) did not detect cortical dysgenesia, or midline development abnormalities. Few focal white matter hyperintensities were observed in the frontal lobes. Unexpectedly, Fast-Field-Echo (FFE) and susceptibility-weighted imaging (SWI) MRI sequences revealed small, round hypointensities in various areas comprising the cerebellar vermis, left occipital regions, left lentiform nucleus, right frontal lobe and parasagittal portion of the posterior parietal gyrus. These lesions, only detected by FFE and SWI MRI sequences, were strongly suggestive of tiny accumulations of haemosiderin adjacent to abnormal fragile microvessels named cerebral microbleeds (CMBs) [4,5] (Fig. 1). As calcium deposits may mimic hemosiderin accumulation [5], we ruled out the presence of calcification by CT scan, thus confirming CMBs.

The combination of a conotruncal heart defect with dysmorphic features and short stature (Table 1) was highly suggestive of typical 22q11.2DS. Array CGH analysis detected a de novo 2.52-Mb hemizygous deletion of chromosome 22q11.2, encompassing nucleotides 18919942-21440514 (GRCh37/hg 19 release).

To the best of our knowledge, this is the first description of CMBs in 22q11.2DS. We investigated the potential risk factors underlying CMBs.

Deep or infratentorial microbleeds usually occur because of fibrohyalinosis due to advanced age and atherosclerosis. However, our patient was young and did not suffer from hypertension (excluded by 24-hour blood pressure monitoring). Another potential factor underlying CMBs is cerebral amyloid microangiopathy (CAA) [4,5], that is characterized by lobar bleeding. Our patient did not display the typical CAA features, which include the strictly lobar distribution and haemorrhagic stroke evidence. We also investigated some of the genes responsible for hereditable CAA (amyloid-beta fragment of amyloid precursor protein, APP; cystatin C; transthyretin and gelsolin) and the APOE haplotype. No mutations were identified; the patient had an e3/e3 genotype, thus she did not carry the alleles predisposing to amyloid deposits in vessel walls (e4) and bleeding (e2).

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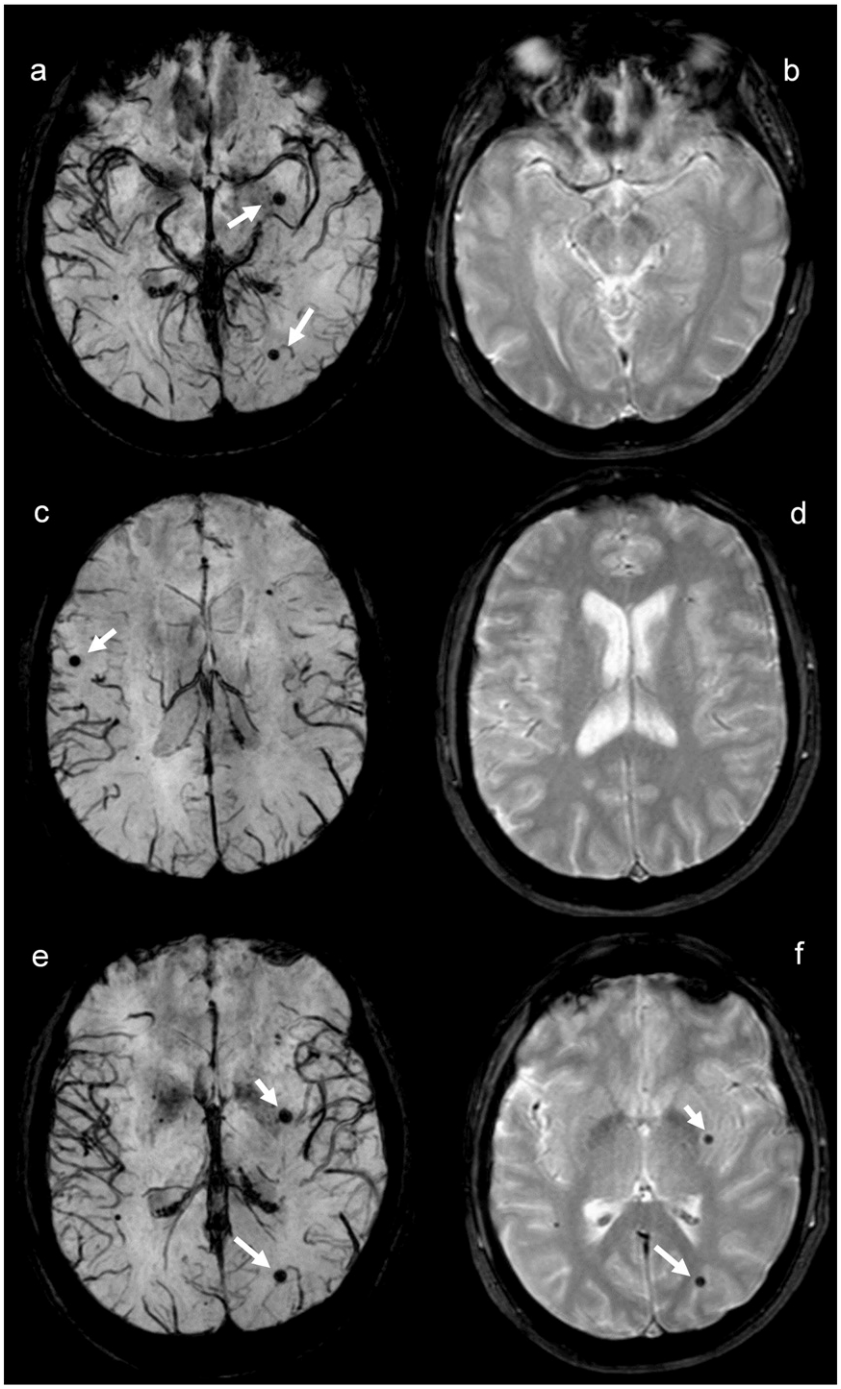

Fig. 1. Images show multiple lesions with hemosiderinic compounds in the brain parenchyma. Axial SWI (a) shows two lesions in the temporal and occipital left lobes and one lesion in the temporo-occipital right lobe, whereas axial FFE (b) doesn't show any lesion. Axial SWI (c) shows one lesion in the right precentral gyrus, not visible on the axial FFE at the same level (d), demonstrating the higher sensibility and specificity of SWI sequence in detecting hemosiderinic compounds. Other images show lesions both on SWI and FFE axial sequences, in basal ganglia (putamen) and in cortical subcortical regions. Images were acquired on a 1.5 T MRI (Philips ACHIEVA) and T2 weighted Fast-Field-Echo axial sequences (FFE TR: 794,70 ms TE: 27,62 ms Matrix 191/240) and Susceptibility-Weighted Imaging axial sequences (SWI TR: 35,42 ms TE: 50,42 ms Matrix:256/256) were obtained.

Thrombocytopenia could also contribute to microbleeding. Platelet size and number are slightly aberrant in most patients with 22q11.2DS with idiopathic thrombocytopenia purpura occurring in 4% of the patients [6]. At hospitalization, our patient showed neither thrombocytopenia (Table 2) nor purpura. Nevertheless, we cannot rule out that episodic thrombocytopenia occurred before patient's hospitalization, went unnoticed and contributed to CMBs.

Since no known CMBs risk factor was detected, we can speculate that the hemizygosity of the genes contained in the deleted region could affect the platelet-vessel wall interactions and contribute to CMBs. The deleted region included the GPIbβ gene, which encodes for one subunit of the platelet GPIb-V-IX receptor. This receptor is critical for platelet adhesion under shear stress in atherosclerotic lesion [7] and the loss of GPIbβ function in Bernard-Soulier syndrome (OMIM 231200) results in a severe bleeding disorder. We investigated the haemostasis and detected a mild reduction of both von Willebrand antigen and activity. A platelet function assay (PFA-100) showed prolonged collagen/ADP and collagen/epinephrine closure times. Cytofluorimetric platelet analysis showed a reduced P-selectin expression (Table 2). These results suggested a bleeding-prone status in our