## Intracranial calcification in systemic lupus erythematosus: a rare condition that needs more attention

Sirs,

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterised by multiple autoantibodies that form immune complexes causing damage to multiple organs (1). The central nervous system is one of the major organs affected, presenting in approximately 37% to 95% of SLE patients (neuropsychiatric SLE, NPSLE) (2, 3). There is a high heterogeneity in their symptoms, including headache (58%), cognitive impairment (14–95%), psychiatric abnormalities (>25%), seizures (15%), cerebrovascular events (3–20%), and abnormal movements (1–4%) (2). Various manifestations of neuroradiological lesions were also found in NPSLE, such as infarction, haemorrhage, and inflammatory lesions in the acute phase, and hyperintensities in white or grey matter and brain atrophy in the chronic phase (3). However, intracranial calcification as a manifestation of NPSLE was scarce.

In this study, we report a rare case of SLE with diffuse intracranial calcification, involving basal ganglia, cerebellum, centrum semiovale, and paraventricular whiter matter symmetrically and summarise the clinical characteristics of related case reports.

A 47-year-old woman presented with slurred speech, facial erythema, oliguria and proteinuria for one month. She had a 16-year history of SLE and had been treated with corticosteroid and hydroxychloroquine. Neurological examination revealed an emaciated female with an old malar erythema on the pale face and dysarthria. No paralysis, rigidity, bradykinesia, hyperreflexia, and abnormal gait was found. Routine laboratory examinations revealed anaemia (haemoglobin 76 g/L) and hypoproteinaemia (albumin 26.9 g/L). Serum calcium (1.90 mmol/L, normal range 2.08–2.60 mmol/L) and phosphate (0.74 mmol/L, normal range 0.85–1.51 mmol/L) were slightly lower than normal. Total protein in urine was slightly elevated (302 mg/24h), while urine nitrogen and creatine were within normal range.

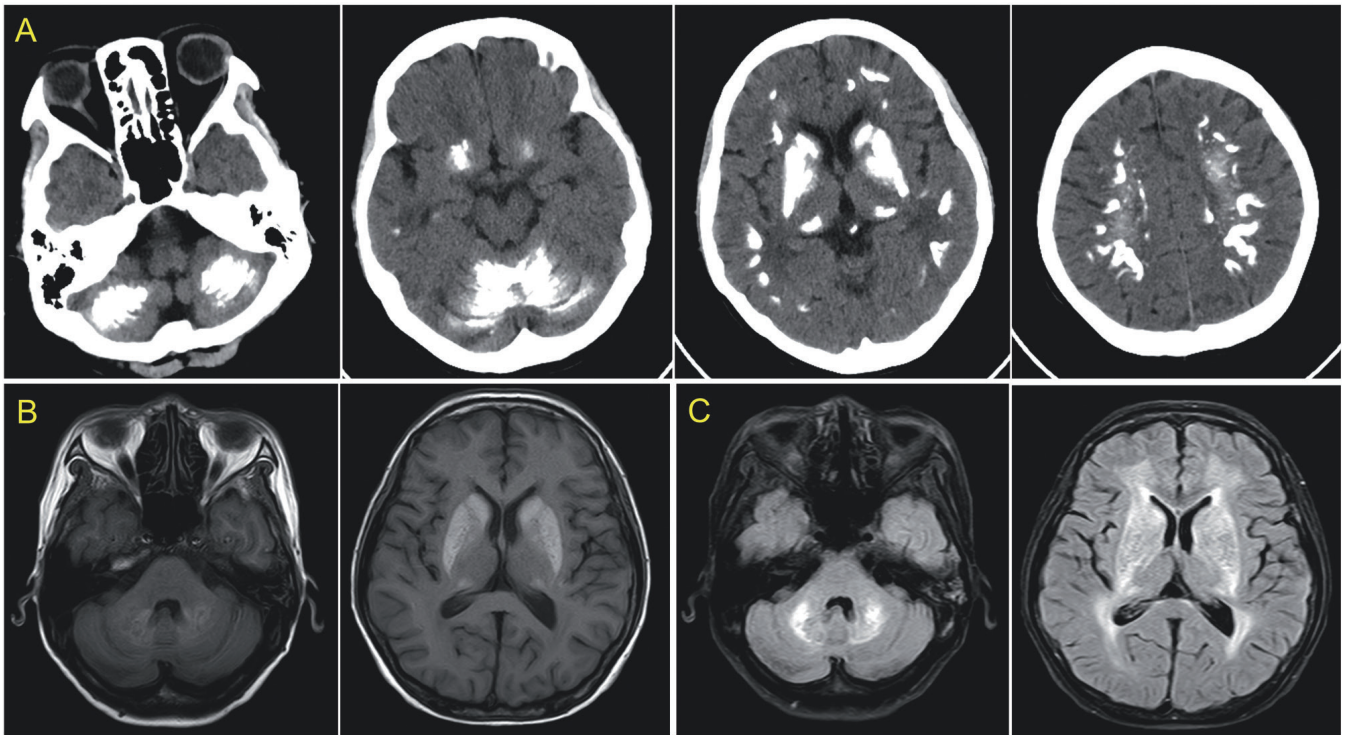


**Fig. 1.** Brain radiologic findings of the patient.
**A**) CT scan showing bilateral symmetric calcifications in the dentate nuclei of the cerebellum, thalamus, basal ganglia, periventricular white matter and centrum semiovale. Brain MRI showing lesions in the dentate nuclei of the cerebellum and bilateral basal ganglia on the **B**) T1-weighted images, and C) FLAIR images.

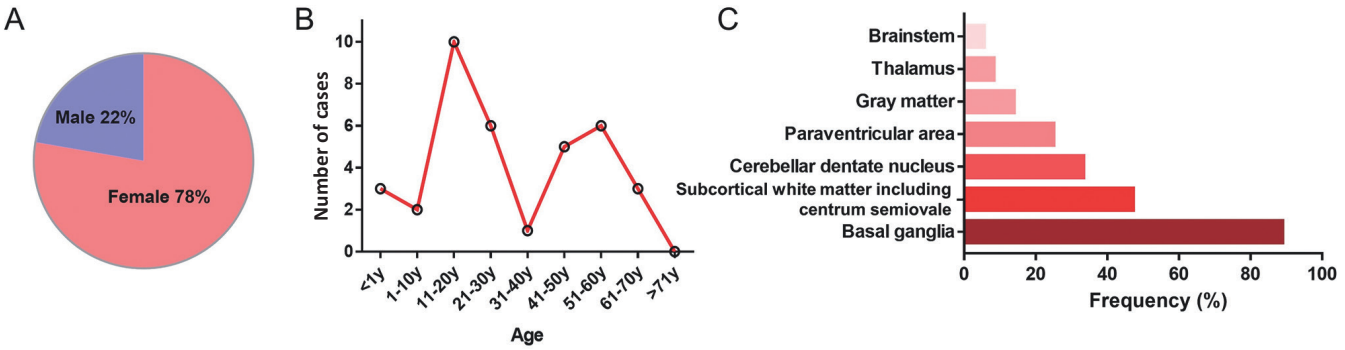


**Fig. 2.** Characteristics of intracranial calcification in SLE. Distribution of **A**) Gender and **B**) Age of SLE cases with intracranial calcification in the literature. **C**) Frequency of SLE intracranial calcification in basal ganglia (88.9%), subcortical white matter including centrum semiovale (47.2%), cerebellar dentate nucleus (33.3%), paraventricular (25.0%), gray matter (13.9%), thalamus (8.3%) and brainstem (5.6%).

Complement C3 was low (0.46 g/L, normal range 0.7–1.4 g/L). Thyroid hormones and parathyroid hormone were normal. Immunologic tests revealed positive antinuclear antibodies, anti-double-stranded DNA antibodies, anti-SSA antibodies, anti-ribosomal P antibodies.

Computed tomography (CT) scan of the brain demonstrated bilateral calcification in the basal ganglia, paraventricular area, white matter of the cerebral hemispheres, and centrum semiovale symmetrically (Fig. 1A). Brain magnetic resonance imaging (MRI) revealed prolonged T1 and T2 signals in lesions found in the CT scan (Fig. 1B-C). No family history of encephalopathy was noticed in this case. A final diagnosis of neuropsychiatric SLE was made and the patient received prednisolone 40 mg daily combined with hydroxychloroquine. 1 month later, her skin rash and slurred speech were alleviated.

Intracranial calcification was rarely reported in SLE and were believed to be unrelated to the severity of neuropsychiatric symptoms (4). The rarity of this condition prompt us to perform a systemic review of related literature. We used "systemic lupus erythematosus", "SLE", "calcification", "calcinosis", "brain", and "intracranial" as keywords searching case reports or clinical trials published in English and found 25 eligible articles including 35 cases (Supplementary Table S1). Like the gender preference of SLE, intracranial calcification has a female predominance (78%) (Fig. 2A). The incidence of intracranial calcification in SLE has two age peaks, one is between 11 and 20 years old, the other is between 51 and 60 years old (Fig. 2B). Among all the reported calcified brain regions, basal ganglia were most commonly affected (88.9%), with fewer cases reporting calcifications in the subcortical white matter (47.2%) cerebellum (33.3%), paraventricular area (25.0%) and (Fig. 2C). Cerebral spinal fluid examination commonly has elevated protein or is not remarkable. Some gene mutations have been found in patients with SLE intracranial calcification, including ACP5, SLC20A2, and SAMHD1 (Suppl. Table S1). However, other complications in those patients made the association between gene mutations and the phenotype complicated.

Differential diagnosis usually includes endocrine causes of abnormal calcium metabolism (such as hypoparathyroidism or pseudohypoprarathyroidism), infectious diseases, neoplastic diseases, and other hereditary neurological diseases such as Fahr's disease. Ordinary screening of serum ions rules out endocrine dysregulation, and etiological examination and cancer related tests can distinguish SLE from infection and cancer associated calcinosis. It's important to distinguish SLE-associated intracranial calcification from Fahr's disease, which is a genetic disorder characterised by abnormal vascular calcium deposition in the movement control area of the brain (5). Fahr's disease commonly has an autosomal dominant inheritance of mutations in several genes such as SLC20A2, DGFRB, PDGFB, XPR1, MYORG, with a predominance between 40 and 50 years old (6). Sometimes, co-occurrence of SLE and Fahr's disease is found in some patients, and they usually have a worse prognosis (Suppl. Table S1). This case did not have a markable family history but had an established SLE. The intracranial calcification was considered to be associated with SLE.

However, the pathogenesis underlying SLE-associated intracranial calcification remains unclear. It is hypothesised that brain calcifications in SLE are partly due to vessel abnormalities, although magnetic resonance angiography did not report significant vessel abnormality in some literature (Suppl. Table S1). It usually takes 2–16 years to develop calcification after diagnosis of SLE (Suppl. Table S1), indicating the chronicity of this disorder. Although the prognosis of SLE has improved substantially in recent years, SLE-associated intracranial calcification continues to provide a significant morbidity and mortality. Early identification of vasculitis or hypoperfusion in CNS of SLE patients may prevent progressive intracranial calcinosis and improve their prognosis. Due to the small sample size and limited follow-up, management of the disease needs further longitudinal study.

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