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Letter to the Editor

Neuronal inclusions and α-Synucleinopathy in a patient with 5p deletion syndrome

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Dear Editor,

1. Introduction

The chromosome 5p deletion (5p-) syndrome, also known as Cri du chat syndrome, is among the most common contiguous gene deletion disorders [1]. Most 5p- cases are thought to arise from a *de novo* deletion; however, 10–15% of 5p- cases are the result of an unbalanced parental translocation. The 5p- classic phenotype includes a characteristic cry, dysmorphic features, growth and developmental delays, while it may present with a wide spectrum of features such as seizures. Neuroimaging studies have shown a few 5p- phenotypic features including microcephaly, hypoplastic brainstem, and partial agenesis of the corpus callosum [2], but neuropathology in 5p- syndrome is rarely described. Here we report a unique case of 5p- with new neuropathological findings that provide insight into the pathophysiology of this disorder.

2. Case report

The patient was an 18-year-old girl with a karyotype of 46,XX,del(5)t(5;12)(p13.3; p11.21) that was inherited from her mother who carried a balanced translocation. She had characteristic 5p- clinical manifestations including a high-pitched cry, severe developmental delay, and intellectual disability with function at a level of less than 12 months old. Her communication strategies were in the pre-verbal stage of development, with cry to express need, and her behaviours were in line with her developmental age. She also had a medical history significant for incomplete right bundle branch block, laryngomalacia, bilateral hip dislocation, chronic constipation, deviated nasal septum, strabismus, poor temperature regulation and scoliosis. Her surgical history included operations for bowel malrotation, gastric tube placement, syndactyly repair, myringotomy for tube insertion, Achilles tendon repair, laparotomy for adhesiolysis and atrial septal defect repair. During the last hospitalization, she presented with a 1-day history of vomiting, and developed increased abdominal distention. Despite resuscitative efforts, she rapidly deteriorated and died in short time.

A complete autopsy confirmed 5p- characteristic dysmorphic features and status post remote surgical interventions. Furthermore, there was a cecal volvulus with acute transmural hemorrhagic infarction of the right colon in addition to acute patchy bronchopneumonia. Subsequent neuropathological examination revealed a few brain abnormalities including microcephaly (with the brain weight of 970 g), olfactory aplasia, focal hypoplasia of the brainstem, partial agenesis of the corpus callosum, cavum septum pellucidum, and polymicrogyria bilaterally in the insular regions (Fig. 1A-C), as well as multifocal neurodegenerative changes with neuronal intracytoplasmic inclusions in the hippocampus and cerebral neocortex (Fig. 1D). Immunohistochemistry showed that those intracytoplasmic inclusions were positive (+) for α-Synuclein (Fig. 1E and F). Tau, β-amyloid, and TDP-43 immunostains were unremarkable. The brain exhibited minimal inflammation without evidence of infection. Electron microscopy demonstrated Lewy-body (LB)-like inclusions in the neurons (Fig. 1G). These neuropathological features suggested α-Synucleinopathy with LB-like pathology.

3. Discussion

The 5p- is occasionally associated with partial trisomy of another chromosome, but the 5p- phenotype is usually predominant. The patient in our present case had 5p- with associated 12p trisomy; however, the 12p trisomy was not phenotypically expressed, despite its phenotypic overlap with 5p- syndrome [3], as macrocephaly and other characteristic features of the 12p trisomy were not observed in this patient. The 5p- phenotype is highly variable, although it classically manifests with a characteristic cry, dysmorphic features, growth and developmental delay. Our present case shows previously reported brain abnormalities such as microcephaly, hypoplastic brainstem and partial agenesis of the corpus callosum, but also previously undocumented findings such as olfactory aplasia, polymicrogyria, and neuronal inclusions with α-Synucleinopathy. These new additions to the 5p- syndrome particularly with α-Synucleinopathy may provide insight into the pathogenesis of neurodevelopmental delay and neurodegenerative changes, as well as a potential therapeutic target of 5p- syndrome.

α-Synucleinopathy in form of intraneuronal inclusions has been a defining feature of a few neurodegenerative disorders such as Parkinson's disease (PD) and dementia with LBs (DLB) [4–6]. α-Synuclein + neuronal inclusions found in our case are reminiscent of cortical

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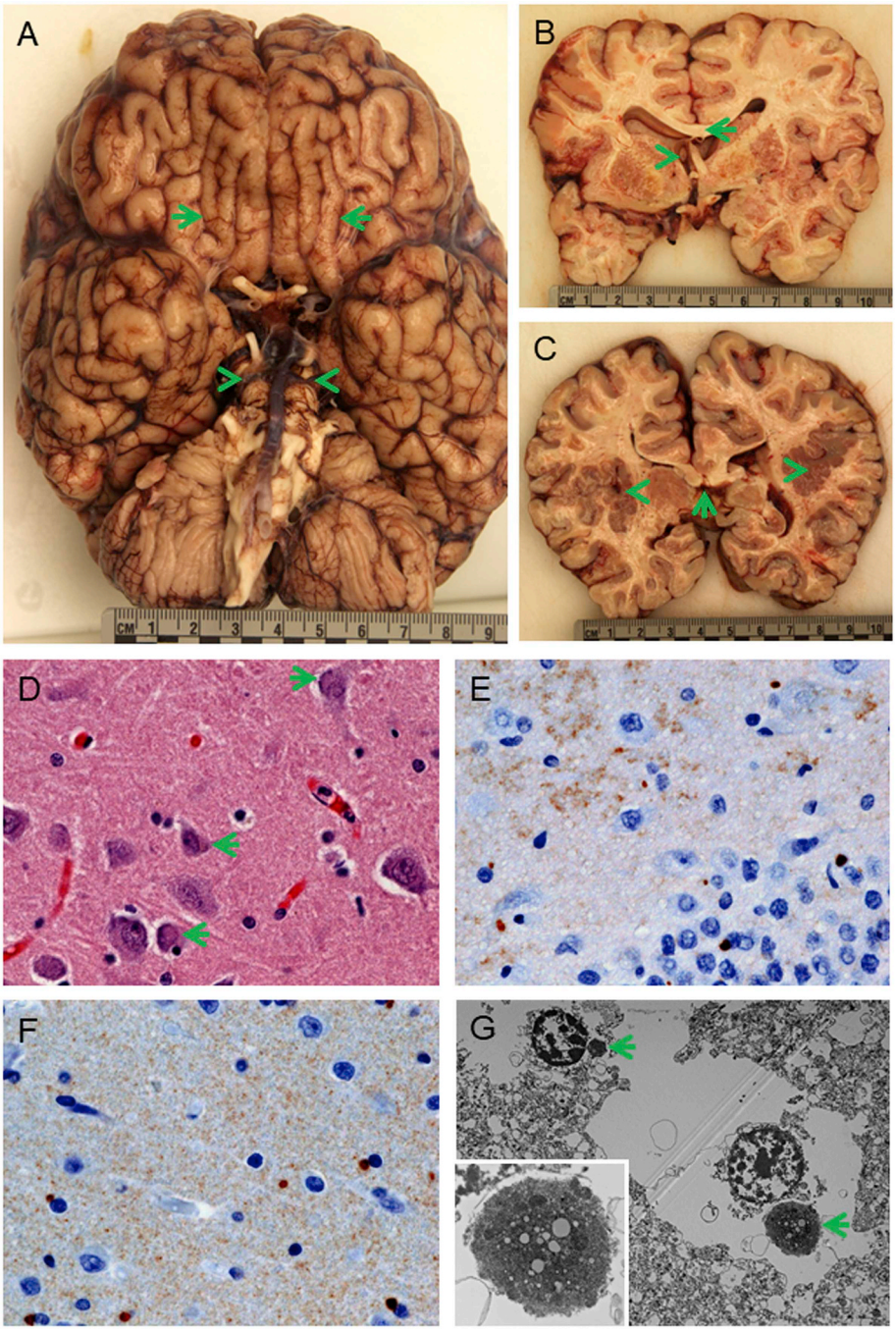

Fig. 1. Brain pathology in 5p deletion syndrome. Macroscopic findings included (A) olfactory aplasia (between arrows) and brainstem hypoplasia (between arrowheads); (B) unremarkable anterior corpus callosum (arrow) and cavum septum pellucidum (arrowhead); (C) partial agenesis of the corpus callosum (arrow, *versus* B) and polymicrogyria (arrowheads). Microscopic examination revealed neuronal cytoplasmic inclusions (D, arrows; Hematoxylin-eosin, original magnification ×400), and α-Synuclein+ inclusions in the hippocampus (E, original magnification ×400) and in the cingulate gyri (F; original magnification ×400). Electron microscopy showed dense inclusions (G, arrows; original magnification ×4000, with a higher magnification inset demonstrating an inclusion).

LBs, although they are generally smaller. These neuronal inclusions, like LBs, are distinctly immune-positive for α-Synuclein and ultrastructurally resemble cortical LBs with granules [5]. It is noted that LBs are also found in a number of neurological disorders including PD, DLB, Alzheimer's disease, and a number of hereditary disorders such as Down syndrome [5–7]. The major component of LBs is α-Synuclein that is a presynaptic, natively unfolded protein with a dynamic balance between monomeric and oligomeric states. α-Synuclein may express its neurotoxic potential when soluble monomers initially form oligomers, then progressively combine to form small protofibrils and further aggregate in large, insoluble α-Synuclein fibrils forming neuronal inclusions such as LBs and those observed in the present case [7,8]. α-Synuclein aggregates in selectively vulnerable populations of neurons and glia are associated with cellular and molecular alternations preceding and accompanying neurodegeneration [4,8]. Despite the need for further research, abundant evidence links the formation of α-Synuclein abnormal filamentous aggregates to the onset and progression of clinical symptoms and degeneration of affected brain regions in neurodegenerative disorders [4,6].

It has been noted that olfactory impairment is an early symptom repeatedly described in the premotor phase of all α-synucleinopathies [9]. Studies have suggested that olfactory dysfunction was associated with an increased risk of PD, and anosmia was commonly reported in DLB and predictive of DLB pathology [10]. Therefore, in our case, the finding of olfactory aplasia is likely related to α-Synucleinopathy and cognitive dysfunction. Also in our case, of particular note is the distribution of α-Synuclein+ inclusions that are specifically in some limbic structures and the paralimbic cortex, which may be related to cognitive, emotional and behavioral dysfunctions in this patient. The topographic distribution of α-Synuclein+ neuronal inclusions in our

case is different from that of typical PD, but overlapping with that of cortical LBs in DLB. Therefore, we hypothesize that the α-Synuclein + neuronal inclusions which pathogenic and clinical implications may be similar to those of other α-synucleinopathies may be associated with at least some of the clinical manifestations such as psychomotor retardation in 5p- syndrome.

In conclusion, the 5p- syndrome seems to be a new member of the α-Synucleinopathy family. The therapeutic approaches targeting aggregated and/or aggregation-prone α-Synuclein, which have been well studied in α-Synucleinopathies [11], may also be a strategy for treatment of 5p- syndrome.

Conflict of interest statement

The authors report no conflict of interest.

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