Movement Disorders
CLINICAL PRACTICE
LETTERS: GENOTYPE AND PHENOTYPE

Brain Calcifications in Complex Sexual Aneuploidy

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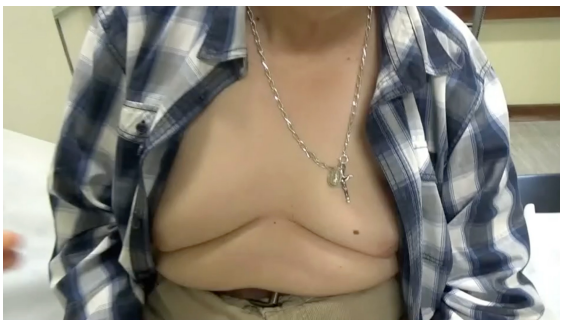
Brain calcifications are commonly observed in routine computed tomography (CT) scans, with its frequency increasing with age.[1,2] Usually symmetrical, small, and located at the globus pallidus, the majority of patients remain asymptomatic.[1] Widespread calcifications are more often secondary and identified in patients with movement disorders or ataxia.[1] Herein we report a patient with brain calcifications whose investigation led to the diagnosis of a rare sexual aneuploidy.

A 68-year-old man first came to our attention at age 64 years. He had a past history of hypertension, diabetes (age 40 years), high cholesterol, and hypoacusia (age 60 years). There was no consanguinity, and maternal history was positive for diabetes and cardiac disease (Fig. S1). As a toddler, "strabismus" was diagnosed, and the patient underwent several ophthalmological surgeries (records not available). Motor development was normal, but a cognitive delay was noticed since early childhood. He performed poorly at school, completing only the fourth grade, and worked under supervision in a family business. At 40 years old, he had a psychotic break and has since been treated with neuroleptics. In his early 50s, an upper limbs tremor emerged as well as slow gait and stooped posture. When first observed (Video 1), he was taking olanzapine 20 mg/day. He had a tall stature, long hands, mild facial dysmorphia (hypertelorism, frontal bossing), sparse facial hair, and gynecomastia. His eyes were misaligned, with left eye abduction, bilateral adduction limitation, and vertical upper gaze palsy not corrected by oculocephalic maneuvers. Perioral chorea was present as well as rest and postural bilateral hand tremor. Asymmetric bradykinesia and rigidity were noticed and were worse on the left. His gait was wide based with bilaterally decreased arm swing and stooped posture (Video 1). On follow-up, bradykinesia and tremor improved with neuroleptics tapering. Bilateral limb dysmetria emerged at age 66, and cognitive performance deteriorated. A head CT disclosed bilateral globus pallidus and small linear corona radiata calcifications (Fig. 1A,B) with correspondent hypointensities on T2* magnetic resonance imaging sequences (Fig. 1C). DaTSCAN was normal (Fig. 1D). Calcium, ionized calcium, phosphorus, and parathormone blood levels were normal. No pathogenic variants were identified on a next-generation sequencing panel for brain calcifications (Appendix S1). Chromosomal analysis was



Video 1. Segment 1 (age 66): here we may observe gynecomastia and facial dysmorphia, with absent motor impersistence on tongue protrusion. The patient has long hands and minor bilateral rest tremor, with mild postural bilateral hand tremor. On finger chase, bilateral dysmetria is present, and bradykinesia is worse on the left hand. Lower limb dysmetria is present on a heel–knee maneuver, and the gait is wide based and slow with decreased arm swing and difficulties with a turning and stooped posture. Segment 2 (age 66): on primary gaze, eyes are misaligned with left eye abduction. On smooth pursuit, there is adduction limitation of the left eye and vertical upper gaze palsy. Saccades are also slow with left adduction and vertical upper gaze limitation. Throughout the video, we observe perioral dyskinesia.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13349

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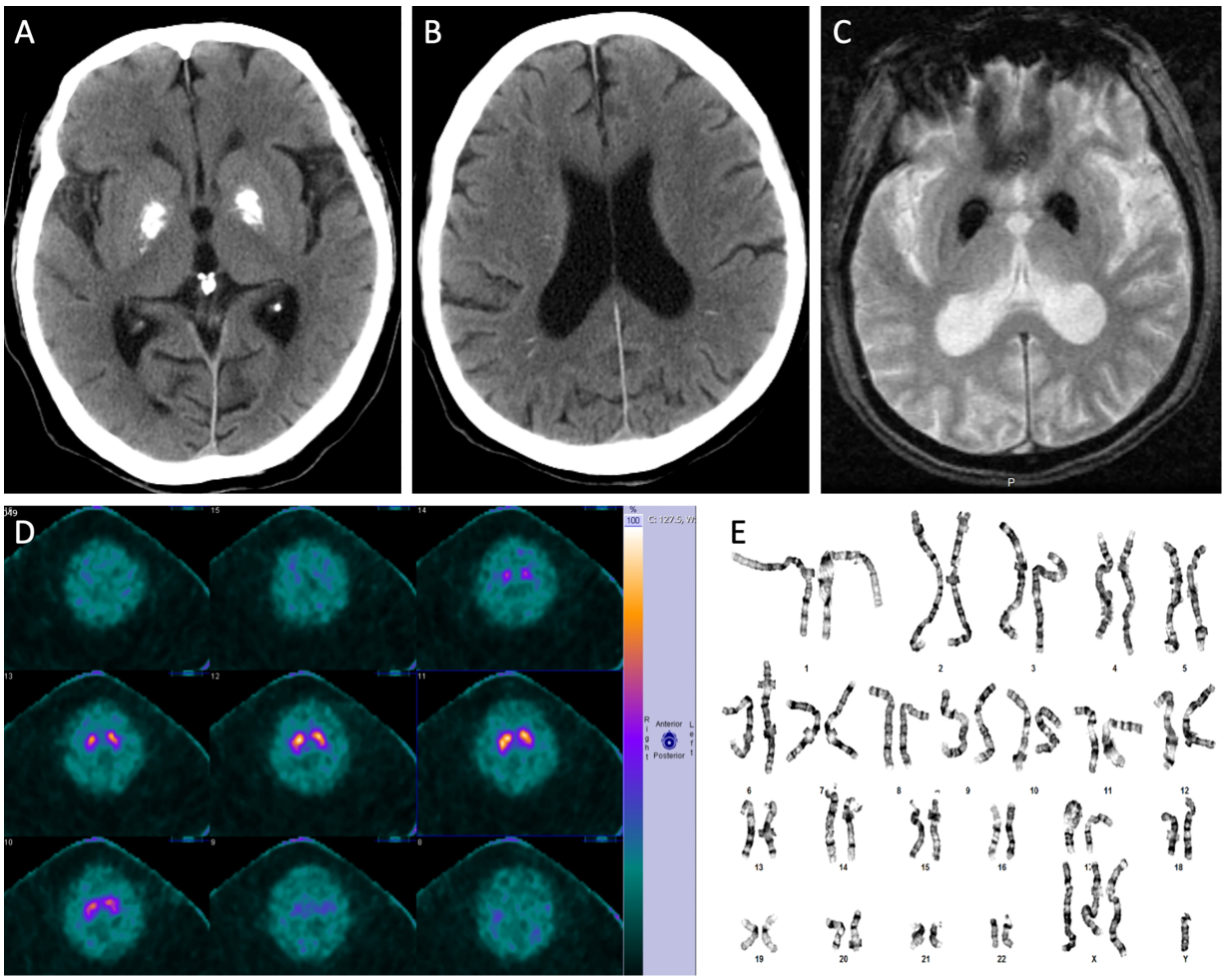

FIG. 1. (**A**, **B**) Head computed tomography: bilateral globus pallidus calcifications and prominent sylvian fissures suggestive of brain atrophy and small linear corona radiata calcifications. (**C**) Brain magnetic resonance imaging: bilateral decreased T2* (gradient echo) signal in the globus pallidus. (**D**) DaTSCAN: normal. (**E**) Karyogram from GTL (G band by trypsin using Leishman Giemsa) banded metaphases: 48,XXXY karyogram.

performed, revealing a 48,XXXY karyotype: mos 48,XXXY [70]/47,XXY[20]/49,XXXXY[3]/51,XXXXXXY[2]/46,XY [5] (Fig. 1E).

Brain calcifications' etiologies encompass a wide list of disorders, with the most frequent being endocrinopathies provoking an imbalance in calcium–phosphorus homeostasis.[1] Other causes include infectious diseases, inflammatory conditions, and neurodegenerative disorders.[1] Idiopathic cases, frequently hereditary, were for decades known as Fahr's disease. An increasing number of genes underlying these familial cases has been described, mostly associated with autosomal dominant inheritance (Table S1).[1]

In the described patient, the presence of cognitive delay, dysmorphia, and female traits were the clues for a chromosomopathy. Hypoacusia and diabetes, with positive maternal history, raised the hypothesis of mitochondrial disorder. This diagnosis was not pursued because diabetes has also been described in sexual aneuploidies[3] and hypoacusia was within the expected for age. Brain calcifications may be present in up to 45% of patients with trisomy 21[4] but are less frequent in sexual aneuploidies. Until now, only 2 patients with Klinefelter syndrome (1 with pseudohypoparathyrodism type Ib, another idiopathic[5,6]) and 3 with Turner syndrome[7,8] have been reported (Table S2). 48,XXXY syndrome is a rare chromosomal condition characterized by 2 extra X chromosomes and has an estimated incidence of 1:50000 male births.[3] It shares clinical features with Klinefelter syndrome such as tall stature, female traits, and hypergonadotropic hypogonadism. This patient had a complex mosaicism affecting the sexual chromosomes, with most cells bearing a 48,XXXY karyotype.

Brain calcifications may be asymptomatic or associated with a wide range of neurological syndromes, the most frequent being parkinsonism, tremor, and dystonia.[2] Cognitive impairment and psychiatric symptoms have also been reported, with cerebellar

and pyramidal signs being less frequent.[2] In our patient, the psychotic episode could be an expression of brain calcifications because it occurred at a later age than expected for "primary" psychosis. A CT scan of that time would be of upmost importance but was not performed. We were most intrigued with his eye movements, resembling an external ophtalmoplegia. One cannot be certain if it were a surgery sequelae or not, but favoring this hypothesis is the absence of progression for 4 years. Parkinsonism and perioral chorea were possibly part of a tardive syndrome in a patient treated with neuroleptics for more than 20 years. A normal DaTSCAN has also been reported in a case of atypical parkinsonism and brain calcifications,[9] but this patient's improvement after neuroleptic tapering favors a drug-induced movement disorder. The absence of visible cerebellar calcifications precludes a relation of late-onset ataxia with brain calcifications, being most likely related to the chromosomopathy.[10]

To the best of our knowledge, this is the first report of brain calcifications in 48,XXXY syndrome. With this description, we wish to highlight the importance of chromosomal studies in patients with brain calcifications, particularly in the presence of dysmorphism or female traits.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

V.O.: 1A, 1B, 1C, 2A
J.P.R.: 1C, 2B
N.O.-T.: 1C, 2B
C.C.: 1C, 2B
J.D.: 1A, 1B, 1C, 2B

Disclosures

Ethical Compliance Statement: a) The authors confirm that the approval of an institutional review board was not required for this work. b) The patient provided a written consent form publication and video. c) We confirm that we have read the Journal's posistion on issues involved in ethical publication and affirm that this work is consistent with those guidelines

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Supporting Information

Supporting information may be found in the online version of this article.

Appendix S1: Gene list.

Figure S1: Family tree: arrowhead, the reported patient; filled symbol, affected individual; slashed symbol, deceased individual; open symbol, unaffected individual; divided black symbol, diabetes and cardiac disease history. Other maternal relatives had diabetes and cardiac disease, which the patient could not identify.

Table S1: Genes involved in brain calcifications.

Table S2: Brain calcifications in patients with sexual aneuploidy.