

Letter to the Editor

Identical twins with Idiopathic Basal Ganglia Calcification (“Fahr’s Disease”) presenting with a remarkably similar pattern of neuroimaging findings

There is a growing interest in defining the genetic background of autosomally dominant inherited Familial Idiopathic Basal Ganglia Calcification (FIBGC), a neuropsychiatric condition often described as “Fahr’s Disease” [1–3].

However, the current debate about the nosology of this heterogeneous phenotype demands a search for standard diagnostic criteria and the identification of loci or mutations responsible for FIBGC that might help to elucidate this intriguing neuropsychiatric condition [4].

The clinical profile includes a variable combination of both motor and cognitive impairment, such as parkinsonism, dystonia, tremor, chorea, ataxia, dysphagia, progressive cognitive impairment, psychosis and changes in mood. Neuroimaging may identify calcifications not only in the basal ganglia but also in the thalamus, cerebral white matter, cerebellum and internal capsule, which are always associated with normal biochemical and endocrine screening [1].

Previous neuroradiological analysis in familial brain calcinosis showed that some individuals may have been symptom free despite the presence of extensive findings on neuroimaging; however, studies measuring the total volume of calcification suggest a significantly larger number of deposits in symptomatic individuals compared to asymptomatic subjects [4].

Linkage of FIBGC to a 13.3-cM critical region on chromosome 14 was described for a large American multigenerational family and this locus (IBGC1) is currently being fully sequenced. Another small kindred, from Spain, has also been reported as possibly linked to this locus, narrowing the candidate region to 10.9 cM; however, various others’ families with IBGC have been excluded from the chromosome 14 region, indicating genetic heterogeneity [2,3].

Here we report a small pedigree with a 53-year-old affected male presenting with a history of Poliomyelitis at 7 years of age and subsequent gait and speech impairment. Ten years ago his symptoms increased rapidly and he presented with parkinsonism associated with mood changes and a computerized tomography (CT) revealed extensive bilateral calcifications in basal ganglia and cerebellum. Unfortunately, the images are not available to us.

The subject is the father of 23-year-old asymptomatic identical twins each with a strikingly similar pattern of CT-scan findings, including calcification of the basal ganglia, white matter and cerebellum (see Fig. 1). All three subjects were investigated for the main metabolic causes of brain calcifications and the idiopathic etiology was ascertained.

These areas of distribution are very typical for IBGC in general; however, previous analysis of familial IBGC shows that the

heterogeneity for this phenotype, even among siblings, is not limited to the clinical outcome but also to the pattern of calcifications distributions [2,4].

This conspicuously similar pattern of calcifications in twins with IBGC suggests a certain level of heritability for the anatomical distribution of calcification depositions and this may be associated with particular disease related loci.

The functionality of the affected brain structures is surprisingly well maintained, despite extensive calcifications. It maybe that the deposits are not the triggering cause for the symptoms but only a sign of progressive underlying tissue damage. We should also consider that calcifications limited to the blood vessels might be a possible explanation for the absence of clinical symptoms in some patients.

Considering that a significantly greater amount of calcification is present in symptomatic individuals, even among subjects from the same pedigree, we might infer that there is a differential level of penetrance for the formation of calcifications and the manifestation of the first symptoms [4].

The issue of differential levels of penetrance has already been addressed in other movement disorders such as primary torsion disease (PTD) and Huntington Disease (HD). While both these conditions are characterized by autosomal dominant inheritance, they also present with variable penetrance. Compared with the HD carrier state, only a minority of mutated dystonia gene carriers ever develops clinical symptoms. Abnormal metabolic findings in the brains of asymptomatic carriers show that our definition of genetic penetrance based only on visual clinical examinations may be flawed, when dealing with hereditary movement disorders with probable metabolic endophenotypes [5].

We conclude that it is necessary to consider two levels of penetrance in IBGC: one for the calcification formations and another for the clinical manifestation. A crucial step towards the definition of this hypothesis will be the identification of a gene or genes involved in FIBGC.

It will be also necessary to perform a follow-up of asymptomatic subjects with calcifications, in order to detect the exact timing of the appearance the first symptoms and to define the limits of brain resilience to calcifications.

The search for genetic loci associated with IBGC is currently defining genetic candidates for this complex neuropsychiatric condition and will be the determining factor for the definition of its physiopathology [1,4].

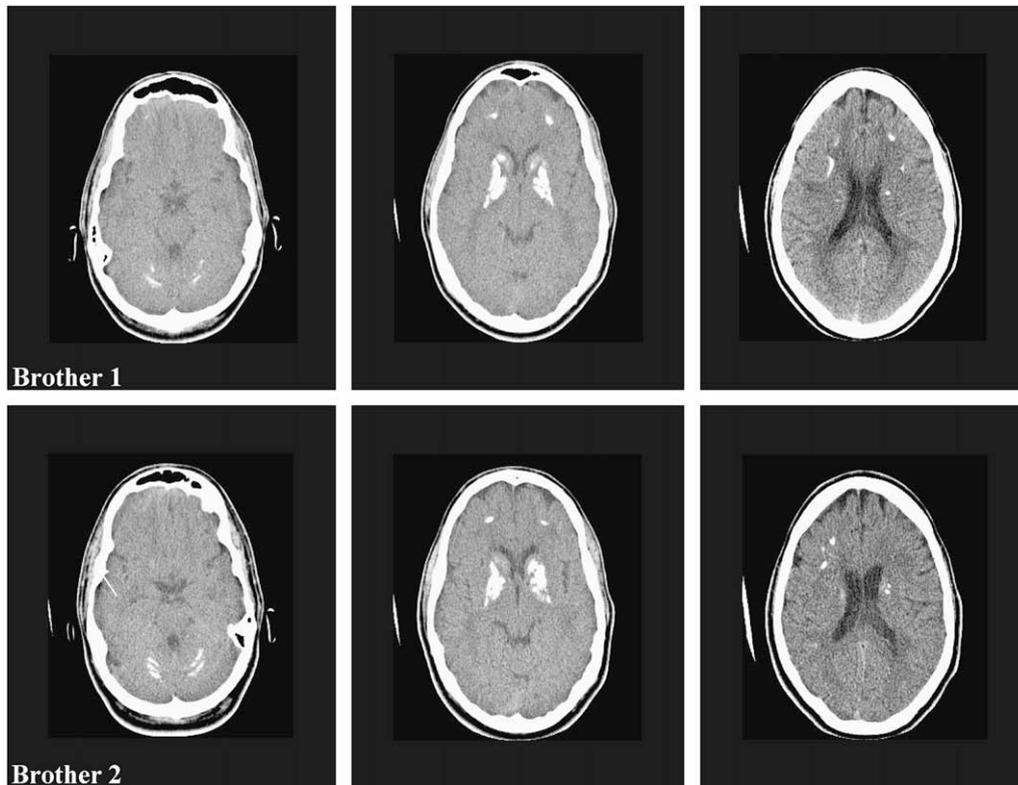


Fig. 1. The axial head computerized tomography showing calcifications in cerebellum, basal ganglia and white matter in the brains of the identical twins in both up and bottom rows.

References

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