Familial idiopathic cerebral calcifications

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SUMMARY Nine members of a family spanning three generations showed bilateral calcifications of the basal ganglia with autosomal dominant inheritance. Two members developed chorea, dementia, and a characteristic speech disturbance (palilalia) in the third or fourth decade. A third member possibly shows the initial stage of a similar syndrome. Six members with calcifications but without neurological signs are younger than 25 years. All nine patients had normal calcium and phosphorus, and no evidence of endocrinological or somatic abnormalities. This 'idiopathic' picture must be differentiated from hypoparathyroidism and pseudohypoparathyroidism.

Bilateral calcification of the basal ganglia is most commonly found in hypoparathyroidism, idiopathic or postsurgical, and pseudohypoparathyroidism. Other causes are toxoplasmosis, encephalitis, and tuberous sclerosis (Holt and Dickerson, 1952; Bennett *et al.*, 1959; Babbitt *et al.*, 1969). Some cases occur in families without endocrinological abnormalities and are referred to as bilateral, familial, cerebral calcification of the basal ganglia. The purpose of this paper is to describe three generations of a family in which nine members show radiological evidence of bilateral calcifications of the basal ganglia, normal serum calcium and phosphorus levels, no clinical or somatic features of pseudohypoparathyroidism (PHP) or pseudopseudohypoparathyroidism (PPHP), and autosomal dominant inheritance. Two members of this family have been described in an earlier report (Boller *et al.*, 1973).

Case reports

FAMILY

The genealogical tree of this family is shown in Fig. 1. The proband's grandparents (Row I) emigrated to the United States from Sweden about 1910. Both died in their 60s without a history of neurological abnormalities. They were not consanguineous.

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Fig. 1 Genealogical tree of the family showing an autosomal dominant mode of inheritance

Case II-1 was in normal health until her mid 40s when she had a gradual onset of speech and movement disorders. When seen 10 years later at age 54 years, her general medical examination, height, body build, and appearance were normal. Neurological examination showed a fairly severe dementia. She was not aphasic, but her speech was characterised by compulsive repetition of phrases and words (palilalia). She showed choreic movements of the head, tongue, and limbs. Her gait was unsteady. Serum calcium was 2.25 mmol/l and serum inorganic phosphorus was 1.45 mmol/l. Cerebrospinal fluid (CSF) total protein was 0.61 g/l; otherwise, the CSF, including the serology, was normal. The skull

Familial idiopathic cerebral calcifications

radiograph showed bilateral calcification of the basal ganglia, cerebral and cerebellar gyri, and of the dentate nucleus of the cerebellum. Radiographs of hands and feet were normal. A pneumoencephalogram showed minimal dilatation of the lateral ventricles and cerebral sulci. A right brachial arteriogram was normal. The patient's speech disorder, chorea, and gait disturbance worsened during the following months. She died about a year later, a few days after a generalised motor seizure. Necropsy was not performed.

Case II-2 had no neurological abnormalities. Skull radiographs showed no intracranial calcification.

Case III-1, a 43 year old housewife, is the oldest daughter of case II-1. When seen for the first time in August 1971, neurological examination was normal. Some time later, however, her daughters and her attending physician noticed that her speech was becoming slightly slurred. This had developed gradually, and the patient was apparently unaware of it. She continued to perform her household and social duties without any apparent difficulty. The neurological examination by one of us (JG) in August 1973 was normal with the exception of mild dysarthria manifested mainly by difficulty in repeating polysyllabic phrases and a somewhat expressionless facial appearance with little spontaneous facial movement. Her memory, speech, and intellectual performance were within normal limits, and there was no evidence of a movement disorder. Her skull radiograph showed extensive intracranial calcification with dense calcification within the basal ganglia bilaterally, curvilinear calcifications bilaterally over the cerebral cortex, and linear calcifications in the posterior fossa, some of which appeared to outline the cerebellar folia. A serum calcium determination had been normal on two occasions.

Case III-2 started to show abnormal movements and speech disturbances at age 36 years. When seen at 39 years of age, his general physical examination was unremarkable. He had some intellectual deterioration (Wechsler Adult Intelligence Scale full-scale IQ of 71). His speech showed striking palilalia. He showed continuous facial grimacing and choreo-athetotic movements of his neck and limbs. The rest of the neurological examination was normal. Serum calcium ranged from 2.6–2.3 mmol/l with a mean of 2.45 mmol/l. Serum inorganic phosphorus, repeated several times, was normal with a mean of 1.13 mmol/l. CSF total protein was 0.53 g/l on one occasion and 0.49 g/l on a repeated tap. The CSF was otherwise normal. An electroencephalogram was normal. The brain scan showed increased uptake of isotope at the periphery of the posterior view on the right, and was interpreted as a questionably positive scan.

Skull radiograph (Fig. 2) showed extensive

Fig. 2 Skull radiograph of case III-2 at age 39 years. There is extensive calcification of the basal ganglia, of the cerebellar dentate nucleus, and of the cerebral and cerebellar sulci.

calcification in the basal ganglia bilaterally, in frontal, parietal, and cerebellar gyri, and in cerebellar dentate nucleus. Angiography of both carotid and the right vertebral artery was normal. Pneumoencephalography showed a mild ventricular dilatation without evidence of gross atrophy of the caudate nucleus.

When seen again in 1973, his speech, intellect, choreic movements, and gait deteriorated to the point that his family could no longer care for him; he is now in a nursing home.

OTHER MEMBERS OF THE FAMILY

Case III-3 shows no neurological abnormalities, and a radiograph of his skull is normal. His son, 3½ years old (IV-7), has been examined and shows no neurological abnormality, but a skull radiograph has not been obtained.

Cases IV-1, 2, 3, 4, 5, and 6, the other six children, ranging in age from 12 to 23 years, all have bilateral calcifications of the basal ganglia as seen on the skull radiograph of case IV-4 (age 15 years) (Fig. 3). None has a history of neurological abnormality. Neurological examination was normal in all six cases.

SUMMARY OF CASE REPORTS

In this family, chorea, dementia, and speech disturbances developed in two members with basal ganglia calcification in their third or fourth decade. A third family member, also with an abnormal radiograph, shows dysarthria and bradykinesia, and is possibly in the initial stage of a similar syndrome. Two members without calcification have reached their fourth decade without abnormalities. Finally, six members younger than 25 years of age have calcification but no neurological sign or symptom.

Discussion

Symmetrical calcification of the basal ganglia appears in many diseases, but in the present case the autosomal dominant heredity limits the differential diagnosis to a few entities. Tuberous sclerosis, autosomal dominant in some instances, is accompanied by intracranial calcification which appears like nodular lesions on the skull radiograph, usually in close relationship to the walls of the ventricle, sometimes present in the basal ganglia (Holt and Dickerson, 1952). Patients with this disease, however, show characteristic skin lesions and often tumours in the kidney, heart, eyes, lungs, and spleen. The pneumoencephalogram is usually abnormal. The appearance of the calcification, and the absence of skin and other systemic lesions in our family practically rule out the diagnosis of tuberous sclerosis. Hallervorden-Spatz disease is sometimes associated with mineral deposits in the basal ganglia, but the heredity and clinical pictures are quite different from those encountered here (Wigboldus and Bruyn, 1968).

Bilateral basal ganglia calcification is a prominent feature of so-called Fahr's disease (1930). This is, however, a misnomer because Fahr's short report on the pathological findings was not the first to describe this entity which had been reported as far back as the mid-nineteenth century (Delacour, 1850). Also, subsequent work has shown that this is not a disease but a group of entities which include hypoparathyroidism,

Fig. 3 Skull radiograph of case IV-4 at age 15 years. There is bilateral calcification of the basal ganglia. No calcification is visible in the posterior fossa or in the cerebral sulci.

Table Number of patients affected, pattern of inheritance, and neurological signs of nine families from the literature and the present family

Author	Number of cases with calcifications	Number of cases with symptoms	Pattern of inheritance	Neurological signs				Notes		
				Impaired mental status	Disorder of speech	Seizures	'Pyramidal' signs	'Extra-pyramidal' signs	Ataxia	
Babbitt <i>et al.</i> (1969)	3	2	D	X		X	X			Children 3-4 years old
Bruyn <i>et al.</i> (1964)	2	2	R	X	X		X		X	Short stature
Foley (1951)	3	1	D	X	X					
Fritzsche (1935)	3	3	R	X	X	X	X			Short stature, CP
Matthews (1957)	2	2	R	X	X		X			
Moskowitz <i>et al.</i> (1971)	5	2	D	X	X					
Palubinskas and Davies (1959)	2	1	D	X	X	X	X		X	
Sala and Savoldi (1959)	2	2	R	X		X				
Schafroth (1958)	5	5	D	X	X			X		CP
Present family	9	3	D	X	X			X		

D = Autosomal dominant. R = Autosomal recessive. X = Symptom or sign present. CP = Consanguineous parents.

PHP, and PPHP (Lowenthal and Bruyn, 1968). PHP and PPHP are familial but are characterised by distinct somatic features and, in the case of PHP, by abnormalities of serum calcium and phosphorus (Lowenthal and Bruyn, 1968). A few families are comparable to ours—that is, they have calcification of the basal ganglia, normal blood calcium and phosphorus levels, and no evidence of endocrinological or somatic abnormalities. A total of only nine families (ours excluded), including 27 members, fits into this 'idiopathic' category (Fritzschke, 1935; Foley, 1951; Matthews, 1957; Schafroth, 1958; Palubinskas and Davies, 1959; Sala and Savoldi, 1959; Bruyn *et al.*, 1964; Babbitt *et al.*, 1969; Moskowitz *et al.*, 1971). Some caution must be exercised concerning the cases of Fritzschke (1935) and Bruyn *et al.* (1964) in which the affected cases had abnormally short statures and may, therefore, have been *formes frustes* of PPHP. The Table summarises some of the clinical data concerning the patients in the nine families from the literature, and in the present family. As can be seen, 20 out of 27 patients with calcifications showed neurological signs. The patients without signs were, however, often younger than those affected, and might have developed neurological signs later in life. The pattern of inheritance is autosomal recessive in four cases, autosomal dominant in the other cases. In the present family it is clearly autosomal dominant. Of the neurological signs, impaired mental status (rarely mental retardation, more often dementia) is uniformly present. Impaired speech, usually consisting of dysarthria, is also uniformly present, except in the case of Babbitt *et al.* (1969) where the mental status of the two young patients was so severely impaired that they apparently failed to develop language. Palilalia was not present in any of these families (nor in any other previously reported familial condition). Seizures are reported in four families. 'Pyramidal' signs consist of unilateral or bilateral weakness with spasticity and increased reflexes. 'Extrapyramidal' signs usually consist of features of Parkinsonism—that is, tremor, rigidity, mask-like facies and so on. Schafroth (1958) fails to mention the nature of the 'extrapyramidal' signs shown by his patient. Only Moskowitz *et al.* (1971) report the occurrence of choreoathetotic movements similar to those observed in our patients. Ataxia was seen in three families. One of the features of the clinical symptoms found in the literature is the great variability found not only between different families but also between patients belonging to the same family. At least two factors can be thought of to explain this variability: one is the part of the brain predominantly affected by calcifications, the second is the age at which patients are examined.

In the family reported here, the youngest member to show calcification is 12 years old. We do not know

at what age calcification became apparent, but it seems that heavy calcification of the basal ganglia precedes the clinical syndrome by several years. If we compare the skull radiograph of case IV-4, who is 15 years old and has no symptoms, with that of his father, case III-2, who developed symptoms in his late 30s, we see that the latter has calcification not only in the basal ganglia but also in the dentate nuclei of the cerebellum, and in the cerebral and cerebellar sulci. It is, therefore, likely that in this condition, deposition of mineral in the brain continues through young adulthood. The appearance of symptoms around the fourth decade may coincide with a critical point at which the calcifications begin to interfere with neuronal function.

The term 'calcification' must be used with caution in this family. There is evidence that in some cases the material is not only calcium, but manganese (Smeyers-Verbeke *et al.*, 1975), magnesium (Bruyn *et al.*, 1964), iron (Moskowitz *et al.*, 1971), and other materials. Treatment with a chelating agent has not been successfully used so far; determination of the chemical nature of the minerals seen on the radiograph is a prerequisite of any possible therapy.

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