Autosomal Dominant Early Childhood Seizures Associated with Chondrocalcinosis and a Mutation in the ANKH Gene

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**Summary:** We describe the pattern of early childhood seizures within a family with autosomal dominant chondrocalcinosis (CCAL, which causes adult-onset arthritis). All affected family members with CCAL experienced seizures in early childhood, usually, but not always, associated with fever. Similarities exist to the syndrome of generalized epilepsy with febrile seizures plus (GEFS+). A mutation within the ANKH gene on chromosome 5p has been found previously in this family; other patients with familial CCAL (but without seizures) have mutations in the same gene. ANKH codes for a transmembrane protein involved in the regulation of extracellular pyrophosphate ion levels, although its precise mechanism of action remains unclear. It is highly expressed in the brain, and its expression may be influenced by seizure activity. The mutation within this family creates a premature initiation codon, adding four amino acids to the N-terminus of the protein. We postulate that this may lead to a gain of function, causing seizure susceptibility as well as chondrocalcinosis. Mutations within this gene may underlie other forms of genetic epilepsy and febrile seizures. Key Words: Chondrocalcinosis—ANKH—Childhood seizure.

Chondrocalcinosis (CCAL) is a relatively common form of arthropathy characterized by the abnormal deposition of calcium pyrophosphate crystals in articular cartilage. The majority of cases are sporadic, although rare familial forms have been described. In 1991, Doherty et al. (1) described several autosomal dominant families, one of which displayed perfect concordance of a childhood seizure disorder with CCAL. In this family, CCAL tended to occur in early adulthood, resulting in recurrent painful acute self-limiting attacks of crystal-associated synovitis, particularly in the knees. The gene was mapped to chromosome 5p15 (2), and mutations were subsequently demonstrated in the ANKH gene in this and other CCAL families (3).

ANKH is the human homologue of the mouse Ank gene, responsible for the progressive ankylosis phenotype. The gene encodes a multipass transmembrane protein involved in regulation of levels of inorganic pyrophosphate in the extracellular compartment (4). Progressive ankylosis in mice results from homozygosity for a mutation that produces a highly truncated (and presumably nonfunctional) protein. These mice develop widespread calcification of articular cartilage and bony outgrowths. In addition to expression in articular cartilage, Ank also is widely expressed in the brain, particularly in the thalamus, midbrain, and spinal cord, and expression is influenced by seizure activity (5). It is therefore an ideal candidate for a seizure-susceptibility gene. The mutation (-11C>T) in our family is 11 base pairs upstream of the normal ATG translation initiation codon. It creates a functional alternative initiation codon, resulting in a four-amino acid addition (methionine-alanine-glycine-threonine) to the highly conserved N-terminus of the protein (3). We have revisited the history of seizures within the family to describe the phenotype and to clarify the role of ANKH in seizure disorders.

**SUBJECTS AND METHODS**

Subjects were derived from a large English family previously reported by Doherty et al. (1). Seizure information was gathered by using a standardized questionnaire, patient interviews, and through access to medical records where appropriate. All subjects gave their informed consent to participation. This study was part of a wider study approved by the Research Ethics Committee of Queen’s University Belfast.
Case Report

The following is a brief account of the clinical course of one member of the kindred (III.3 in Fig. 1) and is fairly typical. The first son of normal nonconsanguineous white parents, he had no symptoms until age 10 months, when he experienced several seizures during a brief febrile illness. These resolved with no sequelae and were described as simple febrile seizures. No recurrences were seen until age 22 months, when he had a further febrile illness. Over the course of 3 days, he had multiple generalized tonic–clonic seizures progressing to status epilepticus, which was treated in hospital. After resolution of this acute episode, he was treated with long-term sodium valproate (VPA) and had no further seizures. An EEG was performed 1 week after the acute episode. The report is as follows:

The record shows an irregular symmetrical but asynchronous mixture of frequencies at 4 to 6 Hz. This activity is more or less continuous throughout the record. The amount of slow activity varies from time to time. There is a good deal of artefact. Some low-voltage fast activity is seen bilaterally. Photic stimulation evoked no abnormality. Conclusion: the record is within normal limits for the age of the child.

On discharge from hospital, he was found to have a mild lack of motor coordination, which persists (age 27 years). He remained well until his early 20s, when pain developed in his knees. A diagnosis of articular chondrocalcinosis was made radiologically.

RESULTS

The pattern of seizures in affected members of the kindred is shown in Figure 1. Both febrile and afebrile seizures were reported. Many were prolonged, requiring hospitalisation, whereas others were more benign, resembling simple febrile seizures. Some individuals reported just a few seizures over a short period (weeks), whereas others had many seizures over a 3- to 4-year period. Precise numbers and details of seizures were often unavailable, as in most cases, considerable time had elapsed since seizure offset. In many cases, old hospital records had been destroyed. More recent cases had often been managed relatively conservatively; the few cases with EEGs had not shown any abnormality. No imaging data were available.

In all cases, seizures resolved completely by age 4 years. Neurologic development was normal in the majority of cases, apart from four individuals: motor incoordination developed in one, whereas three were reported to have learning disability. In one of these latter cases, severe measles encephalitis had developed at age 3 years, followed by substantial developmental regression. No other neurologic sequelae were found in other subjects, and apart from chondrocalcinosis, all reported family members are otherwise healthy.

DISCUSSION

The clinical picture in this family is of autosomal dominant, benign, self-limiting seizures, occurring between the ages of 8 months and 4 years, usually, but not always, associated with fever. The number of seizures reported varied greatly between subjects, some experiencing only a few, in one brief cluster, whereas others had ongoing seizures for a number of years. Seizures were usually benign in that they resolved without any neurologic sequelae. They also were age limited, in that no subject had seizures after age
4 years, and most had resolved by 2 years. This disorder is distinct from simple familial febrile seizures, as evidenced by the large numbers of seizures in several individuals, the prolonged nature of some of the seizures (developing in some cases into status epilepticus), and the occurrence of afebrile seizures in other subjects. The clinical description is limited somewhat by the unavailability of accurate contemporary medical records in many subjects, and the heavy reliance on parent and patient recall.

The seizure syndrome bears similarities to generalized epilepsy with febrile seizures plus (GEFS+), in that many of the seizures were reportedly linked to episodes of fever. However, in GEFS+, many patients go on to experience seizures in later childhood and adulthood (6), whereas in all individuals in this family, seizures stopped before age 4 years. The characteristics of the seizure disorder in this family suggest that it may form a distinct age-limited subgroup of GEFS+.

It is interesting that other families with CCAL have not been reported to exhibit a seizure phenotype. This may indicate that the precise mutation in this family has a particular effect that is not necessarily seen in all CCAL families. This is plausible, because the mutation adds four amino acids to the N-terminus of the protein, possibly creating a specific gain-of-function. This change was not seen in analysis of >200 control chromosomes (3) and is different from other mutations reported in CCAL. Notably, the N-terminus of the ANKH protein is highly conserved in evolution, suggesting that its role is critical to its function. Yepes et al. (5) observed upregulation of Ank after the induction of limbic seizure activity in rats, suggesting a possible role in neuronal excitation and the epileptic process. It is possible that the mutation observed in this family leads to supranormal levels of pyrophosphate or nucleoside triphosphate in the extracellular compartment, resulting in an alteration of neuronal membrane excitability and a predisposition to seizures. Anecdotally, the severity of seizures does not appear to relate to the severity of chondrocalcinosis, but this is difficult to establish firmly because of the young age of several of the subjects and the possibility of inaccuracies in the recall of seizure events from many years ago in older subjects. Further work will be required to characterise the precise effects of the −11C>T mutation from both the clinical and the molecular perspectives.

To our knowledge, no other familial seizure disorders have been reported in conjunction with chondrocalcinosis, and it is not known whether chondrocalcinosis is over-represented in the population of patients with seizures. ANKH also has been implicated in the skeletal disorder cranioectodysplasia (CMD; OMIM 123000) (7), but we did not find any reports suggesting that patients with this condition have a predisposition to seizures.

Progressive ankylosis mice are not reported as having an increased seizure susceptibility. The mutations in these phenotypes are, however, likely to have very different functional consequences from those described in CCAL families.

It remains possible, though unlikely, that the ANKH gene is simply in tight linkage with a separate gene responsible for the seizures. This is unlikely; the linkage data (2) constrain the critical interval for the causative gene to the 3.5 Mbp between the markers DSS810 and DSS416. A number of interesting alternative candidates exist on 5p15, including FBXL7 (which contains leucine-rich repeats, which lies within the critical linkage region) and BASP1 (brain-abundant, membrane-attached signal protein 1, which is outside the critical region); these have not yet been investigated. A recent genome-wide screen (8) of idiopathic generalized epilepsy revealed several loci, including one at 5p15, the same chromosomal region as ANKH, although this finding has yet to be replicated. These issues may become clearer as other families with 5p-linked seizures are studied.

This report adds ANKH to the list of genes involved in idiopathic seizure disorders and suggests that pyrophosphate metabolism may be an important avenue of further research into seizures, both febrile and afebrile. Other genes involved in pyrophosphate handling may themselves be candidates for familial epilepsy and febrile seizures.

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REFERENCES