Novel familial cases of ICCA (infantile convulsions with paroxysmal choreoathetosis) syndrome

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ABSTRACT – Epilepsy and paroxysmal dyskinesia are two episodic cerebral disorders that can share a common genetic basis. Rare families with infantile seizures and paroxysmal dyskinesia [predominantly paroxysmal kinesigenic dyskinesia (PKD)], co-inherited as a single autosomal dominant trait, have been described (infantile convulsions with paroxysmal choreoathetosis; ICCA syndrome) and a disease gene has been mapped at chromosome 16p12-q12 (ICCA region). We report the clinical picture of seven previously unreported families with ICCA syndrome. The identification of novel ICCA families should contribute to better knowledge regarding the clinical manifestations of ICCA syndrome as well as the search for the underlying genetic defect(s).

Key words: infantile seizures, epilepsy, paroxysmal dyskinesia, ICCA syndrome

The relationship between human epilepsies and non-epileptic cerebral disorders, whether paroxysmal (migraine, episodic ataxia, paroxysmal dyskinesia, paroxysmal kinesigenic dyskinesia), or non-paroxysmal (autism, speech impairment, mental retardation), has long been known. In a given family, two or more of these cerebral disorders may be variably co-inherited as a single trait, indicating that common genetic mechanisms may underlie at least the pathogenesis of a subset of these clinically different entities. For instance, mutations in the sodium/potassium channel pump...
gene ATP1A2 have been found in patients with infantile seizures with hemiplegic migraine (Vannmolkot et al., 2003).

Beginn infantile seizures (BIS) are afebrile seizures which commence at age 3-12 months and are associated with a favourable outcome and a normal psychomotor development. Typical seizures are brief with motor arrest, deviation of the head and eyes to one side, generalised hypertonia, cyanosis, and limb jerks. Seizures are focal with or without secondary generalisation and usually occur in clusters. In most cases interictal electroencephalogram (EEG) is normal while ictal EEG shows abnormalities that may originate from various cerebral lobes. Familial forms with autosomal dominant inheritance, namely benign familial infantile seizures (BFIS) and non-familial forms (referred to as BIS), have been reported (Vigevano et al., 1992; Caraballo et al., 2003; Caraballo, 2007).

Paroxysmal dyskinesia (PD) is a rare disorder characterized by the episodic occurrence of involuntary abnormal movements which manifest as attacks of choreoathetosis or dystonia. They are clinically and genetically heterogeneous and various classifications have been proposed (Bruno et al., 2004). Paroxysmal non-kinesigenic dyskinesia (PNKD) can be due to mutations in a gene (MR1) of unknown function (Lee et al., 2004), while three genes for paroxysmal kinesigenic dyskinesia (PKD) have been mapped to 1p34-p33 (PKD with episodic ataxia and spasticity; Auburger et al., 1996), 16p11.2-q12 (Bennett et al., 2000), and 16q13-q22.1 (Valente et al., 2000). More recently, mutations in the SLC2A1 gene encoding the glucose transporter GLUT-1 were found in patients with PD of the exercise-induced type (Suls et al., 2008, 2009; Weber et al., 2008).

The relationship of PD with epileptic seizures has long been suspected (Pryles et al., 1952; Hudgins and Corbin, 1966). In 1997, genetic linkage to chromosome 16 of a newly defined syndrome (infantile convulsions and paroxysmal choreoathetosis, ICCA) demonstrated that typical infantile seizures (i.e. afebrile seizures with onset at age 3-12 months and a favourable outcome) and PD might share common molecular mechanisms (Szepetowski et al., 1997). Since then, several studies have confirmed the importance of the ICCA locus at chromosome 16 (Szepetowski, 2007; Rochette et al., 2008). In addition to the rare large families that independently led to significant LOD scores for each (Szepetowski et al., 1997; Lee et al., 1998), cumulative LOD scores have also indicated linkage to human chromosome 16 in small to medium-size ICCA families with infantile seizures and PD (Tomita et al., 1999; Bennett et al., 2000; Swoboda et al., 2000). To date, the identity of the ICCA gene remains unknown. The diagnosis and collection of data from additional families with ICCA syndrome will help future screening strategies; from classical sequencing approaches to the search for large-scale rearrangements such as deletions and duplications (Rochette et al., 2008). In the present study we describe seven geographically dispersed families with features of ICCA.

**Patients and families**

The seven pedigrees are depicted in **figure 1**. Inclusion criteria for this study included familial association of IS (afebrile seizures with onset at age 3-12 months without recognized aetiology and with a favourable outcome) with PD. Age at onset, neurological examination, type of PD, as well as characteristics of epileptic seizures, were evaluated in all paediatric patients and, whenever possible, in their affected relatives. Interictal EEGs were also performed in the patients according to the international 10-20 system. Clinical family studies were performed when relatives gave informed consent according to local regulations.

**Results and discussion**

**Family 1**

Patient II.3, of French origin, was first diagnosed with recurrent afebrile seizures at age 18 months. At eight years old, she was referred to the specialized clinic for attacks triggered by sudden movement that lasted for a maximum of 30 seconds and could be as frequent as ten per day. The attacks started with transient irregular twitching of the upper extremities. Typically, the paroxysms consisted of dystonic posturing affecting the trunk in a convex manner followed by ballistic movements. At the same time, she had the sensation of “pins and needles” in both feet while maintaining full consciousness. Her brother (II.1) presented with the same clinical picture of PKD at ten years of age but had no known history of epilepsy. Both the children had normal interictal EEG as well as normal radiological and neurological findings. Their mother (I.2) had afebrile epilepsy when she was two to three years old with a favourable outcome and never displayed abnormal movements.

**Family 2**

All the patients in this French family experienced benign infantile seizures before 12 months and all displayed PKD with onset between nine and ten years of age. Seizures were partial with secondary generalisation and were characterised by head and eye deviation, cyanosis and bilateral limb jerks. Attacks of dyskinesia were brief (less than two minutes), occurred more than ten times a day on average and were precipitated by sudden movements.

**Family 3**

Patient III.1 developed afebrile recurrent seizures at age five months when she presented seven seizures during a period of 36 hours. Three seizures were recorded by video EEG monitoring. These seizures were partial with secondary generalisation. The patient responded well to
low doses of carbamazepine and has been seizure-free with normal development since then. In this family of French origin, patient III.2 also had three seizures at age four months; low doses of carbamazepine had the same efficacy with complete stoppage of the seizures. The father (II.2) also had similar seizures at age six months and received phenobarbital for six months. He had episodes of paroxysmal dystonic (non-kinesigenic) choreoathetosis that sometimes lasted for more than one hour, later in life.

Figure 1. Seven novel pedigrees with ICCA syndrome. The asterisks indicate the patients with blood samples collected with the corresponding available DNA. IS: infantile seizures; PD: paroxysmal dyskinesia.
Family 4
Patient II.2, from India, had afebrile seizures in infancy. Onset of brief spells (less than a minute) appeared at age 23 years triggered by sudden movements such as standing up to answer the telephone or when starting to run. Stress, fatigue and hunger were reported by the patient to be aggravating factors. The spells included both choreoathetotic and dystonic movements and were well controlled with 200 mg of phenytoin/day. His brother (II.3), who was reported to have a similar phenotype, and his daughter (III.1) developed infantile convulsions at age three months. Investigations of the daughter were normal, including brain MRI and EEG.

Family 5
The index case (III.1) was a Turkish female presenting with episodes of involuntary abnormal movements that corresponded to attacks of choreoathetosis or dystonia, at four years of age. The attacks were brief (less than a minute) and consistently started with initiation of rapid movements like “jumping up to get the phone”. The attacks were primarily choreoathetotic with some dystonia. Her sister (III.2) had a very similar disorder with onset at age eight years. Their father (II.2), uncle (II.6), and cousin (III.4) were reported to have the same phenotype. Seizures in both girls were well controlled with 100mg of carbamazepine/day. Neurological workups were completely normal including MRI. All patients in the family had benign infantile convulsions between the ages of four months to three years.

Family 6
Patient III.2 was a Malaysian male with mixed Chinese-Caucasian origin. He had uncomplicated antenatal, intrapartum and postnatal histories with normal development. At four months of age, he presented with recurrent afebrile seizures. Further investigations were normal. The patient responded well to phenytoin, which was stopped at age 10 months without further recurrence of seizures. The patient presented again at age eight years complaining of ‘numbness’ of the right forearm. Paroxysmal kinesigenic choreoathetosis was diagnosed. The episodes had increased in frequency and occurred almost daily. These were precipitated by unanticipated sudden movement, with his right arm stuck in a dystonic posture that lasted for a few seconds. His mother (II.4) also had similar symptoms starting at around six to seven years of age. She described her lower limb as being stuck in an abnormal posture associated with irregular jerking, spreading to her upper limb and face. Again, these were brought on by sudden unexpected movement and could be avoided if she slowed down her movement or planned before executing the movements. Symptoms resolved for many years, and then recurred during her university years in Wales. Extensive EEGs and videotelemetry led to diagnosis of epilepsy and sodium valproate was prescribed as antiepileptic treatment. Her brother (II.1) also presented with an afebrile seizure at three years of age.

Family 7
Patient II.1 was a male of Caucasian-Canadian origin who developed afebrile seizures at the age of 3.5 months. Investigations including EEG were normal. At the age of 10 years he presented with a two-year history of a sensation that his legs were out of control. He began to have problems with standing and initiating movement, loss of balance and tripping. There were episodes of flexing at the elbow, extensor rotation at the shoulder and finger flexion. His face and head also became involved. The episodes occurred five to six times per day and lasted about five seconds. Paroxysmal kinesigenic choreoathetosis was diagnosed. In this Canadian family of Caucasian origin, the sister (II.2) presented with seizures at four months. She began to stumble at age six years, which progressed to “freeze-ups”. At the age of seven years she began to have mild dystonia whilst standing or sitting for a while. She progressed to the same PD diagnosis as her brother.

Inter- and intra-familial variability in the ICCA patients has already been described and is largely sustained by the type of PD (kinesigenic, exercise-induced, or non-kinesigenic). More than 30 families with the clinical characteristics of ICCA syndrome have been described worldwide so far (Pryles et al., 1952; Hudgins and Corbin, 1966; Szepetowski et al., 1997; Lee et al., 1998; Sadamatsu et al., 1999; Tomita et al., 1999; Bennett et al., 2000; Swoboda et al., 2000; Hattori et al., 2000; Thiriaux et al., 2002; Kato et al., 2006; Striano et al., 2006), and seven families are reported here, which have not previously been described. Overall, the seven ICCA families studied here showed a relatively homogeneous association between infantile seizures and PD inherited as an autosomal dominant trait (figure 1). Of note, while the familial presentation of ICCA syndrome may variably include patients with PD, infantile seizures, or both, all patients reported here in the seven families presented with PD had infantile seizures earlier in life. PD was of the kinesigenic type (PKD) in all families but one (family 3: non-kinesigenic type, PNKD). This is in agreement with previous findings, as both the predominance of PKD, as part of the ICCA syndrome, and the possible occurrence of other types of PD have been reported (Guerrini, 2001; Szepetowski, 2007). Hence, patients had spontaneous (PNKD) or exercise-induced (PED) dyskinesia in some ICCA families (Szepetowski et al., 1997), while PD was clearly of the kinesigenic type in other families (Pryles et al., 1952; Hudgins and Corbin, 1966; Sadamatsu et al., 1999; Tomita et al., 1999; Swoboda et al., 2000;
Kato et al., 2006). Interestingly also, the type of PD changed with time in one particular patient of a family with BIS inherited as an autosomal trait (Caraballo et al., 2001). Each separate family detected here was too small in size to enable successful genetic linkage; moreover, DNA from several affected individuals was lacking in most families (figure 1). Although we cannot exclude linkage elsewhere in the genome for a minority of the small ICCA families so far, no ICCA family has ever been excluded from linkage to the ICCA genomic area amongst the 27 families that have been genotyped so far (Szepetowski et al., 1997; Lee et al., 1998; Sadamatsu et al., 1999; Tomita et al., 1999; Bennett et al., 2000; Swoboda et al., 2000; Thiriaux et al., 2002; Striano et al., 2006). Hence, it is very likely that the novel families are linked to the chromosome 16 ICCA area, assuming that the ICCA syndrome is genetically homogeneous. These families will help in future gene and genome screening strategies. Together with better knowledge of the clinical manifestations of ICCA syndrome, they will also help in establishing phenotype/genotype correlations when the genetic defect(s) underlying the ICCA syndrome is identified.

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References


Guerrini R. Idiopathic epilepsy and paroxysmal dyskinesia. Epilepsia 2001; 42 (Suppl. 3): 36-41.


