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Autosomal dominant partial epilepsy with auditory features: Defining the phenotype

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Abstract

The authors previously reported linkage to chromosome 10q22-24 for autosomal dominant partial epilepsy with auditory features. This study describes seizure semiology in the original linkage family in further detail. Auditory hallucinations were most common, but other sensory symptoms (visual, olfactory, vertiginous, and cephalic) were also reported. Autonomic, psychic, and motor symptoms were less common. The clinical semiology points to a lateral temporal seizure origin. Auditory hallucinations, the most striking clinical feature, are useful for identifying new families with this synome.

Keywords

Genetics; Epidemiology; Epilepsy; Auditory; Partial seizures

Recently, a genetic contribution to localization-related epilepsies has been demonstrated by the discovery of several syndromes with mendelian inheritance, the establishment of chromosomal linkage in some syndromes, and, in a few instances, gene identification. In an analysis of a single large family, we localized a gene for autosomal dominant partial epilepsy with auditory features (ADPEAF) to a 10-cM interval on chromosome 10q.[1] Affected family members had well controlled complex partial and secondarily generalized seizures accompanied by auditory auras in 55% of individuals.

The current study provides additional clinical detail on the ADPEAF phenotype in our original linkage family, because our original report restricted description of the partial symptomatology to auditory features. More detailed clinical characterization is crucial for identifying new families with the same syndrome, defining the appropriate phenotype for linkage analysis, and localizing the epileptogenic brain region.

Methods

For the current analysis, we reviewed all screening and diagnostic interviews of affected members in the original ADPEAF family. We collected complete information on seizure semiology from the self-reports of affected individuals and from family members who had

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observed the subjects' events. Descriptions of seizure manifestations were recorded verbatim and divided into major categories (table 1).

Results

At the time of the study, 17 members of the family had experienced seizures. Fourteen of these had only recurrent unprovoked seizures (epilepsy), and the other three had acute symptomatic seizures (two febrile, one alcohol-related). Eleven of those with epilepsy had no identified cause; these were classified as idiopathic/cryptogenic. Ten of the 11 people with idiopathic/cryptogenic epilepsy had focal features at the onset of their seizures. All had secondarily generalized seizures as well. The remaining person had only generalized nocturnal seizures; we were unable to determine whether they were primary or secondarily generalized. Complex partial seizures without secondary generalization occurred in seven members, and simple partial seizures occurred in two. Two-hour interictal EEG recordings were done on eight members with idiopathic/cryptogenic epilepsy, one with remote symptomatic epilepsy, and one with nonfebrile acute symptomatic seizures. None of the EEGs showed any abnormality. Imaging data (CT scans) were available for only three affected members, and none was reported to have any abnormality.

Since 1995, one additional family member has had a single unprovoked generalized tonic-clonic seizure at 11 years of age. Because the seizure occurred during sleep and its onset was not witnessed, further clinical details were not available. This patient was started on carbamazepine and to our knowledge has had no further events. This patient, like all other affected family members, shares the seven-marker haplotype that defines the minimal region containing the susceptibility gene.[1] This patient had been classified as “unknown” in the original linkage study because of his young age and absence of seizures at that time.

Table 1 shows the total number of people who reported each symptom, and the distribution and clustering of seizure manifestations within individual subjects. Most subjects described more than one symptom.

Sensory symptoms were reported most commonly, occurring in 73% (8/11) of subjects. Auditory symptoms were especially common (55%; 6/11), but other sensory symptoms (visual, olfactory, vertiginous, and cephalic) were also reported, both in isolation and accompanying the auditory symptoms. Somatosensory auras were not reported. Autonomic symptoms occurred in 45% (5/11) of patients. Psychic or emotional symptoms were present in 45% (5/11) of patients. Motor symptoms were least common (2/18 = 18%), and dystonic posturing was not reported.

Specific auditory symptoms varied among affected family members (table 2). Some described unformed sounds (e.g., #842), whereas others reported distortions or volume changes (e.g., #903). Two patients reported formed and occasionally quite specific auditory auras (e.g., #111). One subject's description suggested seizures provoked by auditory stimuli (#905). A more complex, possibly cognitive disturbance was reflected in another patient's description (#819).

Postictal features in affected family members were also reviewed, but provided no additional information to aid in localization.

Discussion

Auditory auras: a defining feature

Overall, auditory ictal symptoms are prominent in this family, but so are other sensory symptoms. In most studies, elementary auditory auras are reported infrequently, in general

occurring in fewer than 3% of patients.[2-4] The high prevalence of auditory symptoms in this family (55% of those affected) is therefore remarkable.

In a recent linkage analysis of a large Basque pedigree, a susceptibility gene was localized to a 15-cM interval on chromosome 10q that overlaps with our previously described region by a common 3-cM core.[5] Four of the 11 (36%) affected people in the Basque kindred reported auditory symptoms. The partial seizure manifestations suggested a lateral temporal lobe origin, near the temporo-occipital junction; EEG and SPECT abnormalities also pointed to the temporal lobe as an area of dysfunction. The authors named the syndrome autosomal dominant lateral temporal epilepsy (ADLTE). The overlapping linkage regions and clinical similarity strongly suggest that ADPEAF and ADLTE are the same syndrome, but further studies are needed to confirm this. In the interim, the prominence of auditory symptoms is likely to be useful in the search for new families and identification of a specific mutation.

What is the most appropriate name for this syndrome? We prefer the term ADPEAF (which emphasizes clinical presentation) to ADLTE (which emphasizes brain localization). Although the 1989 revision of the International Classification of Epileptic Syndromes[6] groups localization-related epilepsies by their likely brain localization, etiologic and genetic heterogeneity is likely to be extensive in these groups. Naming this syndrome by its most distinctive clinical feature (auditory symptomatology) is likely to define a less heterogeneous group, although even the presence of auditory symptoms does not ensure genetic homogeneity.

Several other familial temporal lobe epilepsies have been described that are not linked to 10q and have phenotypic characteristics more suggestive of a mesial than a lateral temporal origin.[7,8] Autosomal dominant inheritance has been suggested for two of these syndromes, but there is likely to be considerable genetic heterogeneity within this group, and no linkage has been established.

Auditory auras and other clinical features in family 6610: utility for localization?

In the family we report, a lateral temporal seizure onset zone is suggested by several features: 1) the frequent occurrence of auditory hallucinations[9]; 2) the cooccurrence of ictal vertigo in patients with auditory symptoms (although some investigators have found self-reports of vertigo to be weakly localizing)[3]; 3) the occurrence of visual hallucinations in two patients, which may represent posterior propagation to the occipital lobe; and 4) the relative rarity of motor symptoms typical of mesial temporal onset, such as dystonic posturing[10] and oroalimentary automatisms.[2]

The complexity of the genetic and nongenetic contributions to epilepsy results in a poor correspondence between disease genotype and phenotype. Risk for a single syndrome may be influenced by different genetic mechanisms in different families, and conversely, a single genetic mechanism may influence risk for different syndromes within the same family. Nongenetic (environmental) factors and gene-environment interaction may also play a role. Collaboration between clinicians, epidemiologists, and molecular geneticists will help unravel these complexities. Epidemiologic study designs, specifically familial aggregation studies, can help define phenotypes that reflect a shared genetic etiology. Linkage analysis and eventual gene identification will help confirm what phenotypes are important, in addition to contributing to the refinement of clinical syndrome definition and a better understanding of epilepsy pathophysiology.

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Table 1

Partial seizure semiology in subjects with idiopathic/cryptogenic epilepsy in family 6610

		Individual (n = 11)										
Category	**Symptom**	**111**	**601**	**816**	**818**	**819**	**823**	**826**	**842**	**901**	**903**	**905**
Motor	Focal clonic										+	
	Focal weakness										+	
	Automatisms					+						
Sensory	Auditory	+	+			+			+		+	+
	Visual				+	+						
	Olfactory	+										
	Vertiginous					+						
	Cephalic	+	+					+				
Autonomic	Visceral/epigastric	+	+	+							+	
	Cardiac (palpitations)											+
Psychic/emotional	Fear											+
	Déjà vu							+				
	Panic	+										
	Derealization/depersonalization					+				+		

Table 2

Verbatim descriptions of auditory auras in family 6610

Subject no.	Verbatim description
111	I get ringing or singing in my ears. It gets louder and louder. I can't hear other people. Then I try to fight it off and go lie down.
	Ringing/noise/music in my ears. It gets louder.
	Singing, music, voices—maybe voices that I heard in the past-for a while there I thought it was a specific singer- maybe Buddy Holly ... it gets louder and louder and then I just black out.
	First a ringing in [my] ear—blocks out the outside sound and it's just you and the sounds within you.
601	Ringing noises in [my] ear, felt tingly-headed, knew it was coming . . .
	Sometimes I have hearing problems—a voice very loud, then soft, then loud, then normal. I hear a ringing and it gets louder. I have to wait until it goes away.
819	It would sound like people talking would be talking backwards or something. It was kind of humorous, it seemed stupid, I couldn't make sense of it.
842	I start to hear a humming (like a machine? . . . yes) kind of medium volume and I can't hear anyone talking.
903	It's like a tingling feeling and it's like someone turning the amplifier up on the stereo until it gets so loud I can't hear what people are saying.
	It's like a ringing sound in my ear. It starts in my ear.
905	I hear something in my ears. It could be anything from music to voices to sounds that a synthesizer makes. And then eventually as it gets stronger, that's kinda what I hear. Every time I have a seizure except in my sleep has been auditory . . . from sounds, people's voices, from someone speaking to me face to face or over the telephone.
	I'll pick up the telephone and someone will say “hello” and boom, I have to put down the telephone.
902*	A small noise that increases, [I] can't hear normal talking and know that the seizure is coming.
001†	I started hearing voices, like someone was talking to me. The voices were louder and louder, and the next thing I knew, I ended up in the hospital.
	Whistling or something—it's hard to explain—it's a roar or a sound.
	I had a warning. It's like when they give ether—like you're going out of the world and then you don't hear anything.
	The phone rang and the guy on the other end was talking so loud it triggered a seizure.

*Remote symptomatic seizures.

†Acute symptomatic seizures.