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Original article

Electroclinical characteristics of seizures—comparing Prader-Willi syndrome with Angelman syndrome☆

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Abstract

Prader-Willi syndrome (PWS) and Angelman syndrome (AS) are two clinically distinct neurobehavioral syndromes that are caused by deficiency of gene expression from paternally or maternally derived homologues on chromosome 15q11–q13, respectively. Clinical and genetic heterogeneities are common in both syndromes and they are now regarded as 'sister genetic imprinting syndromes'. This study aimed to describe and compare the electroclinical characteristics of seizures between PWS and AS, and to try to explore the possible mechanisms of epileptogenesis in these two syndromes. Fifty patients with genetically documented PWS and 18 patients with a putative diagnosis of AS were included in this study. These patients were diagnosed on the basis of characteristic physical findings and their neurobehavioral phenotype, as well as cytogenetic and molecular studies. Epileptic seizures were present in 16 of 18 patients with AS, but in only eight of 50 patients with PWS. Using electroencephalography (EEG), the most characteristic findings for AS were rhythmic 2–3 Hz delta waves of high-amplitude that were maximal over the frontal regions, and 3–4 Hz spikes and sharp wave runs posteriorly. These were never seen in PWS. Patients with AS had a much higher incidence of seizures with characteristic EEG findings, similar to those seen in mice that are deficient in a single gene (*UBE3A*) that displays regional brain-specific imprinting in humans and mice. In this series, cases with no detectable cytogenetic or molecular defect at the AS locus displayed similar AS phenotype, seizure severity and EEG abnormalities compared to those with such a defect. Thus, the *UBE3A* gene is presumed to be potentially involved in the epileptogenesis of AS. It is also possible that *UBE3A* and another gene located nearby, γ-aminobutyric receptorβ3 subunit, may interact in some way, and result in the severe epilepsy seen with AS. Some patients with PWS and AS share the common EEG features of persistent high-amplitude 4–6 Hz activity in recordings during sleep, and while awake. The significance of such EEG findings needs further experience to clarity.

Keywords: Prader-Willi syndrome; Angelman syndrome; Genetic imprinting; Epileptic seizures; Electroencephalography

1. Introduction

Prader-Willi syndrome (PWS [MIM 176270]) and Angelman syndrome (AS [MIM 105830]) are two clinically distinct neurobehavioral disorders that are nevertheless now regarded as 'sister genetic imprinting syndromes', because they share the same chromosomal abnormalities of 15q11–q13 [1–3]. PWS was first described in 1956 [4] and is characterized by grossly diminished fetal activity, hypotonia, and feeding problems in early infancy, followed by hyperphagia and subsequent central obesity in childhood. Patients also display hypogonadism or hypogenitalism, short stature, small hands and feet and psychomotor retardation. In addition, there are characteristic facial dysmorphisms including almond-shaped palpebral fissures, a narrow bifrontal diameter and downturned mouth, as well as behavioral problems and a tendeny to develop diabetes in adolescence [4–6]. AS was first described by Angelman in 1965 [7], and is characterized by severe mental retardation, inappropriate laughter, happy disposition, ataxic gait, jerky movements, lack of speech and dysmorphic craniofacial features. The diagnosis of AS is primarily a clinical one that

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can be confirmed by laboratory tests [8]. Epileptic seizures occur in most children with AS, but are rare in patients with PWS [2,9–12]. The purpose of this study was to describe and compare the electroclinical characteristics of seizures between PWS and AS.

2. Methods

2.1. Patients

Fifty patients with genetically documented PWS and 18 patients with a putative diagnosis of AS were enrolled in this study. Clinical evaluation of PWS was performed using the diagnostic criteria of Bulter and Holm et al. [5,6], while AS was evaluated using the criteria of Williams et al. [8]. Genetic studies including high-resolution G-banding, fluorescence in situ hybridization (FISH) and DNA methylation patterning were performed according to the methods of Williams et al. [8].

2.2. Cytogenetics

Peripheral blood lymphocytes (PBL) were cultured using standard procedures. High-resolution chromosome banding analyses were performed using methods that increase the frequency of prometaphase chromosomes [13]. Complete karyotype analysis of G-banded chromosomes (using standard trypsin-Giemsa staining techniques) was performed with close scrutiny for deletions of chromosome 15. In cases in which a deletion was not detected, clinical reassessment determined whether FISH was warranted. Patients with typical presentations of AS or PWS who had equivocal cytogenetic studies were subsequently investigated using FISH.

2.3. Fluorescence in situ hybridization (FISH)

FISH was performed using four PWS/AS cosmid probes that were obtained from Oncor Inc. (Gaithersburg, MD, USA): D15S11, small nuclear ribonucleoprotein-associated peptide N (SNRPN), D15S10, and γ-aminobutyric receptorβ3 subunit (GABRB3). The 15q22 cosmid marker, *myl*, was also used (Oncor protocol). These cosmids (D15S11, SNRPN, D15S10 and GABRB3) hybridize to specific sequences in bands 15q11–q13, which include the PWS/AS critical region [14]. The proposed order of the probes on chromosome 15 is D15S11–SNRPN–D15S10–GABRB [14]. After post-hybridization washing in 2× SSC (300 mmol/l NaCl, 30 mmol/l sodium citrate, pH 7.0) at 72 °C for 5 min, visualization was achieved through a series of enzymatic conjugations by horseradish peroxidase precipitation [15], followed by light microscopy.

2.4. Methylation test

Genomic PBL-derived DNA from patients with no detectable deletion over 15q11–q13, from both cytogenetic and molecular studies, was digested with *Hin*d III/*Hpa* II, separated on 0.8% agarose gels, and analyzed by Southern blot hybridization with the probe PW71 (D15S63) according to the protocol of Dittrich et al. [16].

2.5. EEG studies

EEG was performed for all 18 AS cases and for 26 of 50 PWS cases (eight with seizures, 18 without seizures), both while patients were awake and during normal sleep. Four of these 26 PWS cases were also subjected to EEG-respiratogram polygraphy, because of sleep apnea.

3. Results

3.1. AS findings

Microdeletions in the region 15q11–q13 were identified by high-resolution cytogenetic analysis in 11 patients with AS (group I) (Table 1). No other structural rearrangements such as translocation, inversion, or duplication were detected in this region. FISH studies not only confirmed the 11 cytogenetic deletions, but also identified three other molecular deletions (group II) (Table 1). Four cases yielded no evidence of chromosomal abnormality in this region, at both the cytogenetic and molecular level (group III) (Table 1). Two of these four patients were sisters.

Epileptic seizures had occurred in 16 of 18 patients (89%) with AS (nine out of 11 in group I, all of three in group II and all of four patients in group III). Three patients first experienced febrile seizures in infancy. Other seizure types included atypical absence seizures in 10 cases, myoclonic seizures in nine, generalized tonic–clonic seizures in seven and atonic seizures in three cases (Table 2). All 18 patients with AS displayed EEG

Table 1
Eighteen Angelman syndrome cases diagnosed by cytogenetic and molecular studies

Group	FISH				Seizure cases
	S11	NRPN	S10	GABRB3	
I ($n = 11$)	−	−	−	−	$n = 9$
II ($n = 3$)					$n = 3$
1	+	−	−	−	
2	+	+	−	−	
3	+	−	−	−	
III ($n = 4$)	+	+	+	+	$n = 4$

I, High-resolution cytogenetic deleted group; II, high-resolution normal, FISH deleted group; III, no deletion/UPD/methylation abnormalities group; *n*, number; ' − ', deleted; ' + ', non-deleted by FISH.