A new paradigm for West syndrome based on molecular and cell biology

Mitsuhiro Kato

Department of Pediatrics, Yamagata University School of Medicine, 2-2-2 Iida-nishi, Yamagata 990-9585, Japan

Received 28 December 2005; received in revised form 10 January 2006; accepted 6 February 2006

Abstract

Symptomatic West syndrome has heterogeneous backgrounds. Recently, two novel genes, ARX and CDKL5, have been found to be responsible for cryptogenic West syndrome or infantile spasms. Both are located in the human chromosome Xp22 region and are mainly expressed and play roles in fetal brain. Moreover, several genes responsible for brain malformations including lissencephaly, which is frequently associated with West syndrome or infantile spasms, have been found, and the mechanisms responsible for the neural network disorders in these brain malformations are rapidly being determined. Findings of animal and in vitro studies and mutation analyses in humans are delineating the molecular and cellular basis of West syndrome.

Mutations of the ARX gene controlling the development of GABAergic interneurons exhibit pleiotropic effects including lissencephaly with a strong genotype–phenotype correlation. An expansion mutation of the first polyalanine tract of ARX is more strongly related to infantile spasms than is that of the second polyalanine tract. Although the phenotype of CDKL5 mutation is similar to Rett syndrome caused by MECP2 mutation, the former is characterized by early-onset seizures and association with West syndrome. Lissencephaly caused by LIS1 or DCX mutation frequently results in West syndrome, while lissencephaly due to ARX mutation is associated with the most severe form of epilepsy but never results in West syndrome nor infantile spasms. Both LIS1 and DCX participate in the development of GABAergic interneurons as well as pyramidal neurons, while ARX participates only in that of interneurons. Individuals with lissencephaly due to ARX mutation lack non-pyramidal or GABAergic interneurons. ARX is crucial for the development of GABAergic interneuron, so abnormal interneurons in patients with ARX mutation are thought to be implicated in the pathological mechanism, even though brain MRI is normal. Abnormal interneurons appear to play an essential role in the pathogenesis of West syndrome or infantile spasms, which can be considered an interneuronopathy.

Keywords: West syndrome; Infantile spasm; ARX; CDKL5; Lissencephaly, Interneuronopathy

© 2006 Elsevier B.V. All rights reserved.
1. Introduction

In 1841, Dr. W.J. West first reported a peculiar type of convulsion in his own son. The boy was healthy until four months of age, when clusters of head bobbing began. These progressed in frequency and severity, and his developmental progress was arrested. He exhibited significant mental retardation and died at 20 years of age; an autopsy revealed no cause of death (Lux, 2001). West syndrome is now recognized as an epileptic syndrome in infancy, which is characterized by brief tonic spasms, a peculiar set of electroencephalographic findings termed hypsarrhythmia, and arrest of psychomotor development (ILAE Task Force, 1989). West syndrome is the most common epileptic syndrome causing neurological impairment in childhood, while a significant number of patients with this syndrome exhibit normal development (Riikonen, 2001), indicating that developmental arrest is not obligatory for the diagnosis of West syndrome (Lux and Osborne, 2004). Although the term “infantile spasms” is synonymously and confusingly used for West syndrome, here the author uses the term “infantile spasms” as the clinical diagnosis made based on infantile spasms and hypsarrhythmia on the EEG (Fukuyama, 2001).

Many etiological factors for West syndrome including hereditary and non-hereditary conditions, such as neonatal asphyxia, meningocerebral infections, cerebral dysgenesis, and congenital metabolic disorders, have been reported, and this syndrome is now classified into two groups, symptomatic and cryptogenic. The symptomatic group is characterized by the previous existence of signs of brain damage (psychomotor retardation, neurological signs, radiological signs, or other types of seizures) or by a known etiology (ILAE Task Force, 1989). The cryptogenic group is characterized by lack of previous signs of brain damage and of known etiology. The percentage of patients in the cryptogenic group ranges between 9 and 30% (Matsumoto et al., 1981; Vigevano et al., 1993). On the other hand, an idiopathic group has been proposed, and West syndrome in patients in this group is presumed to have resulted from an age-related multifactorial genetic predisposition (ILAE Task Force, 1992). Familial recurrence of West syndrome without known etiology has been reported with uneven distribution to males indicating X-linked inheritance (Feinberg and Leiby, 1977; Dulac et al., 1993; Sugai et al., 2001). Recently, mutations of two genes, ARX and STK9, have been found in patients with X-linked familial West syndrome (Stromme et al., 2002b; Weaving et al., 2004).
A polyalanine expansion mutation of the ARX gene has also been found in a patient with sporadic cryptogenic West syndrome (Kato et al., 2003). It is important to distinguish patients with a genetic predisposition from those in the cryptogenic group. In this review, the author summarizes and discusses the molecular and biological background of the hereditary form of West syndrome or infantile spasms based on the recent findings of genotype-phenotype analysis and for transgenic mice on the genes causing this syndrome, focusing on cryptogenic or idiopathic West syndrome and symptomatic West syndrome associated with brain malformations (Table 1).

2. Cryptogenic West syndrome

2.1. ARX

ARX (aristaless related homeobox) is a paired class homeobox gene located on human chromosome Xp22.13 and consists of five exons encoding protein of 562 amino acids (Miura et al., 1997; Kitamura et al., 2002). The ARX protein has four polyalanine tracts in which 7–16 alanine residues are sequentially repeated (Fig. 1). Three of the four polyalanine tracts are encoded in exon 2, and the first and second polyalanine tracts are mutation hot spots causing mental retardation and epilepsy including West syndrome (Bienvenu et al., 2002; Stromme et al., 2002a, 2002b). To date, 101 patients from 20 families and 3 sporadic patients with the 24 base-pair expansion in the second polyalanine tract have been reported (Bienvenu et al., 2002; Stromme et al., 2002a, 2002b).

Fig. 1. The structure and domains of the ARX gene. C-peptide or aristaless domain is conserved in prd-like homeoproteins. The original number of alanine residues is 16 in the first polyalanine tract and 12 in the second. The expansion in number of alanine residues mutated in patients with infantile spasms is seven in the first polyalanine tract and eight in the second.

The 24 base-pair duplication in the second polyalanine tract exhibits pleiotropic effects, such as familial or sporadic West syndrome, dystonia or Partington syndrome, autism, and non-syndromic mental retardation, brain cysts, and transsphenoidal encephalocele. Variable phenotypes can be seen in the same family (Turner et al., 2002). On the other hand, expansion of seven repeats of GCG in the first polyalanine tract, 333_{334}ins(GCG), which is thought to expand the first polyalanine tract from 16 to 23 alanine residues, has been reported in 14 patients from three families (Claes et al., 1997; Bruyère et al., 1999; Stromme et al., 2002a; Wohlrab et al., 2005). Mental retardation is common in all male patients with a hemizygous polyalanine expansion of the ARX gene (Table 2). As Partington et al. (2004) have already reported that the second polyalanine expansion causes mild to moderate mental retardation in most cases, while the first polyalanine expansion is strongly linked to severe to profound mental retardation. One-fourth of patients with the second polyalanine expansion have epilepsy, which is not necessarily refractory to anticonvulsants. Association with infantile spasms or West syndrome is rare in patients with the second polyalanine expansion, but is noted in two-thirds of patients with the first polyalanine expansion. Long-term expansion of the first polyalanine tract is associated with a severe phenotype, as noted for the polyglutamine diseases, and the position of the expansion mutation also appears to be related to clinical features. Regarding dystonia, two of eight patients in a family demonstrated “hand fisting” or “continuous spastic jerking movements of arms and hands” (Bruyère et al., 1999), but it is unclear whether this symptom is dystonia. Recently, dystonia has been reported in a family with the first polyalanine expansion (Wohlrab et al., 2005). Since dystonia is less frequently associated with idiopathic mental retardation or epilepsy, it is useful for finding patients with a mutation of ARX. Phenotypes of the first polyalanine expansion should be studied further in a larger series of patients.

Another mutation, total deletion of exon 5 of ARX, has been reported in a boy and his maternal uncle who presented with infantile spasms and severe developmental delay (Stromme et al., 2002b). Their clinical findings and course were more severe than those of patients with expansion of the polyalanine tracts. This observation suggests that truncation mutation causes...
Table 2
Dissociation of clinical severity in patients with expansion mutation of the first polyalanine tract and the second polyalanine tract of the ARX gene

<table>
<thead>
<tr>
<th></th>
<th>First polyalanine tract</th>
<th>Second polyalanine tract</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16 (+7)ª</td>
<td>12 (+8)ª</td>
</tr>
<tr>
<td></td>
<td>14 males from 3 familiesª</td>
<td>104 males from 23 familiesª</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>14/14 100%</td>
<td>104/104 100%</td>
</tr>
<tr>
<td>Mild to moderate</td>
<td>0/14 0%</td>
<td>62/73 85%</td>
</tr>
<tr>
<td>Severe to profound</td>
<td>14/14 100%</td>
<td>11/73 15%</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>16/16 100%</td>
<td>22/91 24%</td>
</tr>
<tr>
<td>Infantile spasms</td>
<td>9/13 69%</td>
<td>5/91 5%</td>
</tr>
<tr>
<td>Dystonia</td>
<td>2/3 67%</td>
<td>26/78 33%</td>
</tr>
</tbody>
</table>

Numbers of patients are those clearly described in the literature.

ª Original (and expanded) number of alanine residues.

b Total number of patients.

more severe phenotypes than polyalanine expansion, and, indeed, null mutations of ARX cause anomalies of the brain and the external genitalia (Kitamura et al., 2002; Kato et al., 2004). X-linked lissencephaly with abnormal genitalia (XLAG) is a malformation syndrome of brain and external genitalia (Berry-Kravis and Israel, 1994; Dobyns et al., 1999a). XLAG consists of anterior pachygyria and posterior agyria with a mildly thick cortex, agenesis of the corpus callosum, dysplastic basal ganglia, and ambiguous or hypoplastic genitalia (Kato et al., 2004). ARX was originally suspected to be the causative gene for XLAG, based on similarity to the phenotype of Arx knockout mice (Kitamura et al., 2002). This suspicion was substantiated later by the following observations in human, that is, ARX mutations have been found in 28 of 29 patients with typical features of XLAG, mostly truncations and missense mutations within the homeobox (Kato et al., 2004). Patients with XLAG exhibit intractable seizures from the first day of life or even in the prenatal period, and their seizures are more severe than those in patients with other lissencephaly syndromes, such as Miller–Dieker syndrome (Kato and Dobyns, 2005). Neuroradiological examination of three XLAG patients revealed three distinct layers of the cerebral cortex constructed with pyramidal neurons alone (Bonneau et al., 2002), suggesting a deficit of interneurons, consistent with the findings for Arx-deficient mice. Mouse Arx and human ARX are expressed at high levels in both dorsal and ventral telencephalon, including the neocortical ventricular zone and germinal zone of the ganglionic eminence, with less intense expression in the subventricular zone, cortical plate, hippocampus, basal ganglia, and ventral thalamus (Miura et al., 1997; Ohira et al., 2002). Male mice deficient in Arx have abnormal differentiation and deficient nonradial or tangential migration of GABAergic (y-aminobutyric acid) interneurons in the ganglionic eminence, neocortex, and hippocampus, as well as abnormal testicular differentiation (Kitamura et al., 2002). Deficiency of GABAergic interneurons is strongly suspected to play a role in the pathogenesis of the most severe seizures in XLAG patients. Interestingly, patients with XLAG exhibit neither infantile spasms nor hypsarrhythmia. Patients with West syndrome or infantile spasms caused by ARX mutation show basically a normal brain MRI finding, which indicates the existence of interneurons in the brain. As mentioned above, ARX is crucial for the development of GABAergic interneuron, so interneurons in patients with ARX mutation are thought to be implicated in the pathological mechanism, even though brain MRI is normal. GABAergic interneurons in the brain might also be caused by disorganization of neuronal networks and can be considered an interneuronopathy (Kato and Dobyns, 2005).

2.2. CDKL5/STK9

The CDKL5 (cyclin-dependent kinase-like 5) or STK9 (serine-threonine kinase 9) gene is located on chromosome Xp22.3 and is causative of X-linked infantile spasms (ISSX) and a variant form of Rett syndrome (Kato et al., 2004).
syndrome (Kalscheuer et al., 2003; Tao et al., 2004; Weaving et al., 2004; Evans et al., 2005; Scala et al., 2005). Although the precise function of CDKL5 is still unknown, except for the phosphorylation activity imputed to it based on its gene structure, the expression of Cdkl5 in mouse brain overlaps that of Mecp2, which is mutated in more than 80% of patients with Rett syndrome (Weaving et al., 2004, 2005). Evans et al. (2005) summarized the clinical features reported for 14 patients with CDKL5 mutations (1) as including seizures early in onset (neonatal to three months of age), presence of infantile spasms (57%), hypsarrhythmia on EEG (29%), and subsequent generalized tonic–clonic seizures and myoclonic jerks refractory to antiepileptic medications. Although epilepsy is seen in 94% of patients with Rett syndrome (Steffenburg et al., 2001), the onset of seizures is usually after one year of age, and infantile spasms have not been reported in association with a MECP2 mutation (Evans et al., 2005). Infantile spasms occupy 90% of seizures in patients with classical lissencephaly, although the EEG may not reveal typical hypsarrhythmia (Guerrini, 2005). Diffuse high-amplitude fast rhythms (8–18 Hz) or extreme spindles and sharp and slow wave complexes with amplitude higher than 500 μV on the EEG are notable findings in patients with classical lissencephaly (Hakamada et al., 1979; de Rijk-van Andel et al., 1992).

LIS1 is expressed in all migrating neurons throughout all periods of development (Meyer et al., 2002), and recently LIS1 has been found to be required for normal non-radial or tangential migration of GABAergic inhibitory neurons as well as for radial migration (McManus et al., 2004). Reduction of calretinin-expressing interneurons in the fetal period is found in the cerebral cortex in Miller–Dieker syndrome, suggesting slowed cell migration inducing disruptions of the timing of axon outgrowth and establishment of neural circuits (Pancoast et al., 2005). Heterozygous deletion of Lis1 causes a 50% reduction of Lis1 protein and disrupts the normal migration of pyramidal neurons, dentate granule cells, and interneurons in the hippocampus of mice (Fleck et al., 2000). This migration defect causes hyperexcitability at Schaffer collateral-CA1 synapses and depression of mossy fiber-CA3 transmission. It also leads to a reduced threshold for interictal epileptiform activity and more intense interictal bursts than in wild-type mice (Fleck et al., 2000). Both a defect in inhibitory neurons and hippocampal abnormalities may explain the epilepsy and mental retardation in patients with lissencephaly caused by a LIS1 mutation.

3.2. Subcortical band heterotopia/Double cortex syndrome

Subcortical band heterotopia or double cortex syndrome (SBH/DCS) is characterized by bilateral continuous symmetric bands of gray matter underlying the
cortical mantle. About 90% of patients with SBH/DCS are female, and this condition is in most cases caused by DCX mutation. Somatic mosaic mutations of DCX or missense mutations of DCX or LIS1 can cause SBH/DCS in male patients (Pilz et al., 1999; Kato et al., 2001). Epilepsy is present in almost all patients (93%) with SBH/DCS (D’Agostino et al., 2002). Mean age at seizure onset is 4–5 years. About half of patients have focal seizures at onset, and the remaining half have generalized or undetermined seizures (Barkovich et al., 1994). The severity of clinical symptoms, including time of seizure onset, intellectual deficits, and neurological examination findings, is significantly related to the extent of pachygyria and degree of ventricular enlargement (Barkovich et al., 1994; Granata et al., 2005). The presence and severity of epilepsy are not strictly related to the severity of neuroradiological findings such as the extent of pachygyria and degree of ventricular enlargement (Barkovich et al., 1994). Epilepsy is intractable in 65–75% of patients with subcortical band heterotopia (Guerrini and Carrozzo, 2001; D’Agostino et al., 2002). DCX is a microtubule-associated protein located in both the leading process and the perinuclear region, and positively regulates the rate of migration of neurons interacting with LIS1 and dynein (Tanaka et al., 2004). DCX is expressed in specific neurons depending on the timing and space of development. The expression of DCX in both radially oriented cells and non-radially oriented calretinin-positive cells in the human fetal brain suggests the involvement of both glutamatergic excitatory neurons and GABAergic inhibitory neurons (Meyer et al., 2002). Hemizygous male Dcx knockout mice, which totally lack Dcx protein, exhibit decreased postnatal viability and abnormal layering in the hippocampus, which is also observed in human patients, but have the normal six-layered neocortex and normal apical and basal dendrites with well-developed spines (Corbo et al., 2002). Recent RNA interference studies of Dcx in mice succeeded in inducing subcortical band heterotopia with disrupted neocortical lamina similar to that seen in human patients (Bai et al., 2003). Heterotopic neurons generated synaptic action potentials produced by local extracellular stimulation, indicating the existence of physiologically functional neurons and synapses (Bai et al., 2003). In human patients with SBH/DCS, functional connectivity and activity of heterotopic neurons and adjacent neocortex have been demonstrated by diffusion tensor imaging and functional MRI (Pinard et al., 2000; Eriksson et al., 2002). These findings suggest that interaction between the apparent normal cortex and heterotopic neurons play roles in epileptogenesis as well as in normal function.

3.3. Schizencephaly

Schizencephaly (cleft brain) is characterized by a full-thickness cleft lined with an infolding of gray matter from the cerebral cortex into the ventricle with fusion of leptomeningial pia mater and the ventricular ependymal layer (Barth et al., 1987). Schizencephaly has heterogeneous etiologies and is divided into two types based on the presence or not of association of polymicrogyria or subependymal heterotopia in adjacent regions. The term “porencephaly” has historically been used to cover all cleft-related abnormalities of the brain, and currently tends to be used for secondary destructive changes after the post-migration period (Hayashi et al., 2002), though many of these are vascular-disruptive in origin (Curry et al., 2005).

The clinical severity of schizencephaly in patients ranges widely from nearly normal to severely handicapped in relation to the extent of defective cortex (Packard et al., 1997). In general, epilepsy is present in one to two-thirds of patients, and is refractory to antiepileptic drugs in less than one-third of cases (Granata et al., 2005). The presence and severity of epilepsy are not strictly related to the severity of neuroradiological findings, such as unilateral or bilateral cleft (Denis et al., 2000). Seizures are mostly focal, and their type is related to cleft location. Infantile spasms and myoclonic or atomic seizures are rarely reported (Granata et al., 2005). Focal epileptic discharges on interictal EEG are consistent with the cleft location. There are several differences in seizure types and EEG findings between unilateral schizencephaly and unilateral polymicrogyria (Caraballo et al., 2004). Continuous spike-wave activity during slow sleep, atypical absence, and epileptic-negative myoclonus indicating
a secondary bilateral synchrony mechanism are exclusively present in patients with unilateral polymicrogyria and not in unilateral schizencephaly (Caraballo et al., 2004). Although the reasons for this are still unknown, schizencephaly is frequently accompanied by polymicrogyria, suggesting a common pathogenesis. The predominantly focal seizures seen in patients with schizencephaly might be related to disconnection of neural circuits by a cleft.

EMX2 is the only gene known to be responsible for schizencephaly, though mutations of it are found only in limited numbers of patients with this condition (Facella et al., 1997; Tietjen et al., 2005). EMX2 is a homeobox gene, and the mouse protein Emx2 regulates neocortical area patterning such as that of the primary sensory and motor areas in cooperation with Fgf8 or Pax6 (Fukuchi-Shimogori and Emx2; Tietjen et al., 2005).

The predominantly focal seizures seen in patients with schizencephaly might be related to disconnection of neural circuits by a cleft.

Acknowledgement

This work was supported in part by a grant from the Japan Epilepsy Research Foundation.

References


