

Compulsive behaviour in a patient with Aicardi syndrome. Agenesis of the corpus callosum

Condotta compulsiva in paziente con sindrome di Aicardi. Agenesia del corpo calloso

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Summary

The corpus callosum, which is the largest white matter structure in the brain of all placental mammals, connects the left and right cerebral hemispheres. An alteration in its morphology, hypoconnectivity or hyperconnectivity is a common marker of various neuropsychiatric pathologies. One of these is Aicardi syndrome, which is characterized by a triad of callosal agenesis, infantile spasms and chorioretinal lacunae. Patients affected by Aicardi syndrome frequently display other malformations together with congenital defects of the eyes, ribs and vertebrae. Based on the current clinical knowledge, this syndrome is now recognized as a complex neurodevelopmental disorder that includes neurolog-

ical and constitutional symptoms. However, literature data have not yet defined the presence of a particular set of symptoms in psychiatric patients with this condition. The present case is the first report in which an on-going compulsive behaviour focused on the insistence to order objects has been observed in Aicardi syndrome.

Key words

Aicardi syndrome • Agenesis of the corpus callosum • Seizures • Compulsive behaviour • Dysmorphism • Mental and psychomotor developmental delay

Syndrome description

Although it is a relatively rare disease, Aicardi syndrome is estimated to affect thousands of people worldwide. The disorder was first recognized as a distinct syndrome by the French neurologist Jean Aicardi in 1965. It is a rare encephalopathic malformation affecting almost exclusively young females and very rarely males with Klinefelter syndrome (47 XXY karyotype)¹⁻³. It has therefore been suggested that Aicardi syndrome may be the direct result of a *de novo* dominant mutation in a gene located on the X chromosome, and lethal in hemizygous males³.

The first sign of the disease becomes evident around the age of three months, when young patients begin having infantile spasms. The triad that characterises Aicardi syndrome includes, in fact, agenesis of the corpus callosum (CC) and pathognomonic chorioretinal lacunae in addition to the above-mentioned "marker"¹.

Based on current clinical knowledge, the syndrome is now recognized as a complex neurodevelopmental disorder characterized by additional neurological and constitutional symptoms.

Indeed, neurological examination may detect microcephaly, axial hypotonia and appendicular hypertonia with

spasticity and deep tendon hyperreflexia as well as a moderate-to-severe psychomotor and mental retardation⁴. Seizures associated with asymmetric spasms, often preceded by partial early-onset epileptic fits in the first three months of life, may also be detected. A third element may be a peculiar EEG pattern characterized by asymmetric activity and asynchronous intercritical paroxysmal anomalies in both hemispheres due to agenesis of the corpus callosum, with an MRI detecting its dysgenesis. Frontal perisylvian polymicrogyria, periventricular and subcortical heterotopia, gross brain asymmetry, choroid plexus papilloma, ventriculomegaly and intracerebral cysts are also frequent findings.

In addition to pathognomonic chorioretinal lacunae, patients affected by Aicardi syndrome present unilateral microphthalmia, coloboma/hypoplasia of the optic nerve, retinal detachment and nystagmus.

Craniofacial, vertebral and costal anomalies are also reported; these include short philtrum, prominent premaxilla with a consequent reduction in the frontonasal angle, large ears, sparse and lateral eyebrows, plagiocephaly and facial asymmetry. The occurrence of hemi-vertebrae, block vertebrae, fused vertebrae and missing ribs is common and can lead to marked scoliosis in up to one-third

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of subjects. These patients may also display an increased incidence of vascular malformations and pigmented lesions⁵.

Gastrointestinal disorders such as gastro-oesophageal reflux, diarrhoea and difficulty in feeding are perceived by parents to be the second most difficult problems to manage after seizures⁶.

Survival is another characteristic that deserves further attention. Life expectancy was originally thought to be rather limited. Today instead, based on recent data from the USA, around 60% of the patients are expected to survive until the age of 27 years, with some cases reaching the age of 40 years. Survival is therefore highly variable and is probably related to the severity of disease.

For these reasons, additional diagnostic criteria have been proposed (Table I)^{5,7}. The interest of the present case lies in the fact that it may confirm a hypothesis, already suggested by several studies, that the CC may play an important role in various psychiatric disorders.

Case description

Patient: 36 years of age (born 16 Jan 1976). Although birth was premature (at the 8th month), she was nonetheless born after a full-term pregnancy. The delivery was long, the amniotic fluid was stained and the umbilical cord was wrapped twice around the newborn's neck. No other maternal diseases were reported during pregnancy. At 3 months she had an epileptic fit characterized by muscular hypotonia and upwards rotation of the eyeballs. The same symptomatology recurred a short time later. The delay of psychomotor development became soon evident, as she managed to sit at 12 months and started walking at 21 months. Language development was also delayed. During this period, she suffered from several

seizures characterized by reduced muscle tone and very brief losses of consciousness that always followed bouts of crying.

For these reasons several EEG were performed (at 7 months, 21 months, 2 years and 3 years of age) which showed among other things a slight anomaly of regulation of electrogenesis and mild abnormalities in the right hemisphere.

Weight gain was very limited. In the course of development she presented a malfunctioning alvulus with frequent, abundant, unformed mucous stools. The patient had dysmorphic features consisting of small forehead, sparse and dry hair, bushy eyebrows, flat nasal bridge, small teeth, fleshy nose, larger-than-normal right ear and a hammer toe. She also had a hypochromic patch on her face and trunk extending to the anterior abdominal wall, two small flat haemangiomas on her back, strabismus (heterotropia) and a pronounced lordosis. Various eye examinations detected severe myopic chorioretinal scarring with retinal chorioretinosis at the posterior pole of both eyes. An instrumental brain examination (MRI) performed in 1992 detected a malformation consisting in agenesis of the splenium of the CC associated with dysmorphism in the back of medial ventricular cells. The last EEG recorded a moderate slowing-down of the base rhythm and graphoelements with transient spikes apparently originating from left frontal derivations.

At the beginning of 2012, she was admitted to the U.O.D. Universitaria di Psichiatria, Ospedale "A. Fiorini" of Teracina for evaluation because she displayed symptomatology characterized by a compulsive behaviour aimed at arranging objects in a symmetrical fashion. The involuntary interruption of this behaviour led to anxiety and irritability, and in extreme cases led to violent reactions. Moreover, since the patient suffered from a syndrome

TABLE I.
Features. *Criteri diagnostici.*

Classic triad	Key features	Supporting features
Agenesis of the corpus callosum	Cortical malformations (especially polymicrogyria)	Vertebral and rib anomalies
Pathognomonic chorioretinal lacunae	Periventricular and subcortical retinal heterotopia	Microphthalmia
Infantile spasms	Frequent brain cysts affecting the third ventricle and/or choroid plexus	"Split-brain" EEG
	Optic disc/nerve coloboma or hypoplasia	Gross asymmetry of the cerebral hemisphere
		Vascular malformations or tumours

The presence of the classical triad is diagnostic of Aicardi Syndrome. The simultaneous presence of two features of the triad and, in addition, of at least two main or support features is strongly suggestive of this syndrome. Based on Sutton⁵.

that involved mental retardation and language delay, it was impossible to investigate any obsession beyond the behaviour itself. A correct interpretation of clinical symptoms was difficult due to the difficulties encountered in exploring the thought content. Moreover, the family's request for treatment was mainly focused on finding a treatment for the dysphoric characteristics, especially in terms of psychomotor restlessness and insomnia. Therefore, the treatment selected included a mood-stabilizer (valproic acid: maximum dose, 750 mg/day; plasma levels of valproate: 61 µg/mL) and a sleep inducer (delorazepam: maximum dose, 1.5 mg/day). These drugs complemented the previous neurotherapy that consisted of carbamazepine (600 mg/day), orfenadine (150 mg/day), biperiden (4 mg/day) and pericyazine (7.5 mg/day). This therapy resulted in a partial remission of dysphoric symptoms and sleep disturbance. Although the compulsive symptoms have not shown any clinical improvement, the additional pharmacotherapy did allow to the possibility to shed light on this psychopathological dimension as being predominant in the patient's mind.

Syndrome-case comparison

Our patient presents symptoms and features that meet criteria for Aicardi syndrome (Table I)⁸. The agenesis of the splenium of the CC and the severe myopic chorioretinitis are suggestive of Aicardi syndrome^{1 2 7}. The onset of symptoms at the age of three months is consistent with literature descriptions, according to which most of the seizures occur in the first three months of life⁷. Likewise, the clinical history shows quite clearly that there is developmental delay in psychomotor abilities⁴. Gastrointestinal disorders, which are among the causative factors of deficits in body weight gain in patients with Aicardi syndrome⁶, began to appear early, at around 18th months. Furthermore, the patient displays dysmorphic features common in this syndrome such as ear asymmetry as well as vascular malformations and pigmented lesions (flat angiomas of the spine and a hypochromic patch extending to the abdominal wall)⁵.

It can thus be inferred that Aicardi syndrome is not limited to the classic triad, but represents a much more complex neurodevelopmental disorder characterized by several neurological and constitutional symptoms.

Psychiatric relevance of the case

One of the features observed in the Aicardi syndrome is agenesis of the CC. This wide, flat bundle, which is the largest white matter structure in the brain of all placental mammals, connects the left and right cerebral hemispheres and contains numerous intra-, and interhemispheric axonal projections.

Callosal fibres connect cerebral areas that are homotopically positioned. Fibres from the inferior frontal lobes and the anterior and inferior parietal lobes cross in the genu, and those from the remaining part of the frontal area and from the parietal lobe cross in the body of the CC. Fibres from the temporal and occipital lobes cross in the splenium (Table II)⁸. Corpus callosum agenesis (CCA), either total or partial, occurs in approximately 14% of central nervous system anomalies. Its typical clinical symptoms are macrocephaly, facial dysmorphism combined with different levels of mental retardation, epileptic seizures, vision and other nerve impairments. Moreover, CCA is associated with Dandy-Walker, Aicardi, Toriello-Carey and Andermann syndromes⁹.

An alteration in the morphology, hypoconnectivity or hyperconnectivity of the CC is therefore a common marker of various neuropsychiatric pathologies such as schizophrenia, bipolar affective disorder, attention deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD)¹⁰⁻¹⁵. This relationship is confirmed by the altered morphology, hypoconnectivity, or hyperconnectivity that all display. For example, Bersani and colleagues have found that schizophrenics have a reduced width of the splenium (which is involved in the transfer of visual information), while Walterfang et al. reported that patients with bipolar disorder have smaller anterior and posterior callosal regions and thinning of the CC¹¹⁻¹³. However, the precise function or dysfunction of this structure in the

TABLE II.

Anatomical organization of callosal subregions. *Organizzazione anatomica del corpo calloso.*

<i>Rostrum</i>	Fronto-basal cortex
<i>Genu</i>	Prefrontal cortex and the anterior cingulate area
<i>Truncus (midbody)</i>	Precentral cortex (premotor area, supplementary motor area), the adjacent portion of the insula and the overlying cingulate gyrus
<i>Isthmus</i>	Pre-and post central gyri and primary auditory area
<i>Splenium</i>	Posterior parietal cortex, occipital cortex, medial temporal cortex
Based on Raybaud ⁸ .	

above disorders remains uncertain. The behavioural abnormalities of several patients analyzed can indeed be attributed, other than to its action, to a secondary effect of dysfunctional cortical regions.

Additionally, the CC has been shown to be involved in attentional processes and has therefore been indicated as a possible cause of ADHD, even though this syndrome does not show similar behavioural changes in split-brain patients. The areas connected by the splenium involve the parietal cortex, which supports functions such as sustained and divided attention. A review by Hutchinson, Mathias and Banich (2008) noted that children and adolescents with ADHD have a smaller splenium compared to control subjects¹⁴.

Finally, the CC might have also a role in OCD. In fact, several diffusion tensor imaging (DTI) studies have previously reported callosal abnormalities in patients with OCD¹⁵. Additionally, a recent examination of axial and radial diffusivity in patients with OCD has shown that the reduced white matter integrity in the CC may be caused by a myelin abnormality. This finding is consistent with preliminary data according to which the polymorphism of a gene that is a major regulator of the development of myelin-producing cells is associated with OCD¹⁶. In some brain regions such as the CC, myelination continues during adolescence and early adulthood, a period during which OCD may easily onset¹⁷.

Neurodevelopmental irregularities leading to abnormal myelination might therefore play a role in the pathophysiology of OCD. However, this hypothesis needs support with longitudinal and postmortem studies.

The literature reports no specific psychiatric symptomatology in patients affected by Aicardi Syndrome. Judging from our observation, the patient described is the first case in which a subject affected by this syndrome displays compulsive behaviour aimed symmetrically arranging objects. In the future, in order to better assess its psychopathological aspects, it would be interesting to find out whether a similar framework is present in other patients with this syndrome. The occurrence of this symptomatology could be a further element supporting the hypotheses about a possible role of the CC in OCD.

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