ARTICLE CLASS OF EVIDENCE

Basal Ganglia Dysmorphism in Patients With Aicardi Syndrome

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Abstract

Objective

Aiming to detect associations between neuroradiologic and EEG evaluations and long-term clinical outcome in order to detect possible prognostic factors, a detailed clinical and neuroimaging characterization of 67 cases of Aicardi syndrome (AIC), collected through a multicenter collaboration, was performed.

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Glossary

AIC = Aicardi syndrome; **CC** = corpus callosum; **EDACS** = Eating and Drinking Ability Classification System; **GMFCS** = Gross Motor Function Classification System–Expanded and Revised; **MACS** = Manual Ability Classification; **TE** = echo time; **TI** = inversion time; **TR** = repetition time.

Methods
Only patients who satisfied Sutton diagnostic criteria were included. Clinical outcome was assessed using gross motor function, manual ability, and eating and drinking ability classification systems. Brain imaging studies and statistical analysis were reviewed.

Results
Patients presented early-onset epilepsy, which evolved into drug-resistant seizures. AIC has a variable clinical course, leading to permanent disability in most cases; nevertheless, some cases presented residual motor abilities. Chorioretinal lacunae were present in 86.56% of our patients. Statistical analysis revealed correlations between MRI, EEG at onset, and clinical outcome. On brain imaging, 100% of the patients displayed corpus callosum malformations, 98% cortical dysplasia and nodular heterotopias, and 96.36% intracranial cysts (with similar rates of 2b and 2d). As well as demonstrating that posterior fossa abnormalities (found in 63.63% of cases) should also be considered a common feature in AIC, our study highlighted the presence (in 76.36%) of basal ganglia dysmorphisms (never previously reported).

Conclusion
The AIC neuroradiologic phenotype consists of a complex brain malformation whose presence should be considered central to the diagnosis. Basal ganglia dysmorphisms are frequently associated. Our work underlines the importance of MRI and EEG, both for correct diagnosis and as a factor for predicting long-term outcome.

Classification of Evidence
This study provides Class II evidence that for patients with AIC, specific MRI abnormalities and EEG at onset are associated with clinical outcomes.

Aicardi syndrome (AIC) is a rare congenital condition, defined with the classical triad (corpus callosum [CC] agenesis, chorioretinal lacunae, and infantile spasms), or on the basis of the Sutton modified diagnostic criteria.[1,2] Affected patients are usually severely neurologically disabled,[3–5] although rare cases with a favorable outcome and a nearly normal neurologic examination are reported.[6,7]

Given the absence of a genetic hallmark or other biomarkers of the condition, in an effort to identify predictors of long-term outcome, we specifically looked for associations between the neuroradiologic and electroclinical features of the syndrome. In a multicenter collaboration, we analyzed clinical and imaging data from 67 patients diagnosed with AIC.

Methods

This multicenter retrospective study involved centers from Italy, France, Switzerland, Denmark, and Germany.

Standard Protocol Approvals, Registrations, and Patient Consents
Written informed consent was obtained from the parents or legal representatives of all the involved patients for imaging studies and clinical evaluation when performed. The study complied with institutional regulations for anonymized retrospective studies and was approved by the ethics committee of the National Neurologic Institute C. Mondino of Pavia (approval number P-20170023685). The study adheres to the principles of the Helsinki Declaration and concerns data gathered during routine diagnostic activity.

Data Availability
Anonymized data that support the findings of this study are available from the corresponding author (P.V.) on reasonable request. Not all of the data are publicly available because they contain information that could compromise children's privacy and their family consent.

Clinical and MRI Data Collection
Only patients who met the Sutton[1] modified criteria for AIC were included in the study: the presence of 2 classical features (CC agenesis, infantile spasms, chorioretinal lacunae) plus at least 2 other major or supporting features is strongly suggestive of the diagnosis.

The study, a cohort study with retrospective data, meets the criteria for Class II evidence: exclusion/inclusion criteria were clearly defined, it includes a broad spectrum of participants,

and disease status was determined objectively and measured in all the participants. The primary research question was to detect in AIC possible associations between neuroradiologic and EEG evaluations and long-term clinical outcome, the latter evaluated with clinical standardized outcome scales, in order to detect possible prognostic factors.

Clinical motor and neurologic outcome data and epileptologic data were collected retrospectively. Clinical motor outcome was classified on the basis of the Gross Motor Function Classification System–Expanded and Revised (GMFCS) and the Manual Ability Classification (MACS)[8]; the neurologic examination was also classified using a scoring system based on clinical evaluation: patients with a normal neurologic examination scored 0, those with slight pyramidal signs 1, hemiplegia or diplegia 2, severe diffuse hypotonia 3, and spastic tetraplegia 4. Taking into account the poor cognitive and language profile of patients with AIC, the following scale was used to measure language: ability to say sentences (Class 0), ability to say single words (Class I), babbling (Class II), vocalization (Class III), none of the aforementioned (Class IV). The Eating and Drinking Ability Classification System (EDACS) was used to assess eating and drinking safety and efficiency.[8] For statistical analysis, seizures were classified as epileptic spasms, focal seizures, multiple seizure types, and status epilepticus, isolated or in variable combinations. Seizure frequency was classified as daily, weekly, and monthly episodes.

Brain MRI and CT imaging data were systematically reviewed according to a protocol used by Hopkins et al.[9] and modified by us (details in table 1). Written reports (referring to 75 brain MRI and 8 brain CT scans) on 67 patients diagnosed with AIC were available. The actual neuroradiologic images (64 MRI and 7 CT) of 55/67 patients were available and systematically reviewed by 2 experienced neuroradiologists; any discrepancies in their findings were resolved by a third neuroradiologist.

MRI studies were performed using different 1.5T scanners according to standard protocols: T1 spin echo sagittal sequences (representative measures: slice thickness 3 mm; repetition time [TR] 500–550 ms; echo time [TE] 8–15 ms), T2 turbo spin echo axial and coronal images (representative parameters: slice thickness 3 mm; TR 5,300–6,000 ms; TE 120–200 ms), fluid-attenuated inversion recovery axial and coronal images (slice thickness 3 mm; TR 8,000–10,000 ms; TE 120–125 ms; inversion time [TI] 2,800 ms), and inversion recovery coronal sequences (slice thickness 3 mm; TR 2800 ms; TE 10–15 ms; TI 400 ms) were obtained. When available, diffusion-weighted imaging data were also reviewed. For statistical analysis, the patients were classified on the basis of MRI features: CC abnormalities were classified as partial/complete agenesis vs hypoplasia. With regard to gray matter involvement and distribution of cortical dysplasia, we distinguished between focal (defined as limited areas of cortical dysplasia), multifocal (defined as multiple but not adjoining areas of cortical dysplasia), and diffuse cortical malformations. The presence of nodular heterotopia was classified by number of nodules (<4 or >4), cysts were classified according to their site (supratentorial, subtentorial, or both, and choroid plexus cysts or papillomas). Posterior fossa abnormalities were classified as mild (e.g., slight inferior vermis hypoplasia) or severe (e.g., cerebellar cortical dysplasia, rhombencephalosynapsis). Figure 1 provides a detailed list of all the imaging measures analyzed and their classification.

The sample was described using standard descriptive statistics: mean and SD or median and interquartile range for continuous variables and proportions for categorical ones. Normality distribution was assessed by the Shapiro-Wilk test. The association between qualitative variables was investigated by Pearson χ^2 or Fisher exact and between outcome scales and explicative variables (neuroradiologic features and EEG evaluations) was studied by nonparametric Wilcoxon rank-sum test. This analysis was then followed by application of Kruskal-Wallis test and post hoc testing, adjusting for multiple comparisons. Statistical significance was set at the level of ≤0.05, unless adjustment for multiple comparisons (applying the Bonferroni correction) was needed.

All analyses were performed using STATA/SE for Windows, version 14.2.

The percentages given in the Results refer to the subsets of patients in whom relevant data were available.

Results

Clinical Phenotype

A cohort of 92 patients with suspected AIC was collected; only 67 of these cases met the classical or Sutton[1] diagnostic criteria and were therefore included in the study. A total of 59 cases were unreported; 8 patients were described in a recent published article.[10] All the patients were female, with an age range of 9 months–27 years (mean age 10.29 years). Five patients were deceased at the time of the study (age range at death 5–28 years). Pregnancy history data were available for 54 cases, and showed complications in 27.78%: threatened miscarriage, maternal hypertension, polyhydramnios, oligohydramnios, placental abruption, reduced fetal movements, hepatitis C virus infection. The mean maternal age was 31.93 years (range 17–42) and the mean paternal age 35.35 years (range 19–51).

In 86.56% of cases, ophthalmologic examination revealed the classical chorioretinal lacunae; in 5 patients, ophthalmologic examination was not available or inconclusive, and in the other 4 it was normal. A total of 33/61 (54.09%) patients showed coloboma, associated with microphthalmos in 5 (8.20%). Five out of 61 patients showed only microphthalmos.

Table 1 Neuroradiologic Results, % (n)

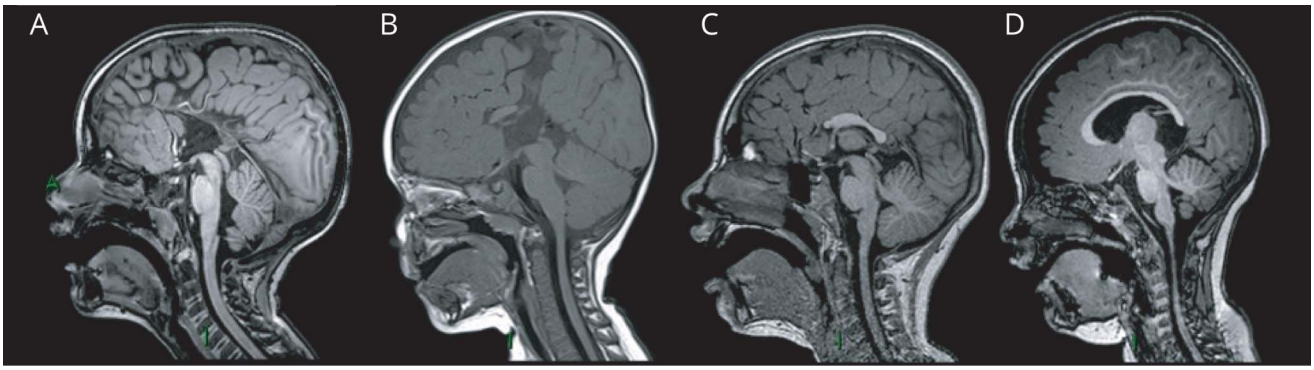
Corpus callosum dysgenesis, 100% (67/67)			Ventricular abnormalities, 96.36% (53/55)		Cortical dysplasia, 98.43% (63/64)				Posterior fossa malformations, 63.63% (42/66)	
Complete agenesis	Partial agenesis	Hypoplasia	Ventriculomegaly	Dysmorphisms	Diffuse	Multifocal	Focal	Not detected	Mild	Severe
50.75 (34/67)	40.3 (27/67)	8.96 (6/67)	61.81 (34/55)	89.09 (49/55)	51.56 (33/64)	35.94 (23/64)	10.94 (7/64)	1.5 (1/64)	42.42 (28/66)	21.21 (14/66)

Cysts, 96.36% (53/55)											Basal ganglia dysmorphisms, 76.36% (42/55)	
Localization				Number			Pattern		Type[a]			
Supratentorial	Infratentorial	Supratentorial and infratentorial	Choroid plexus	Absent	One	≥2–10	Unilocular	Multilocular	2b	2d	Mild	Severe
61.19 (41/67)	8.96 (6/67)	17.91 (12/67)	33.33 (22/66)	3.63 (2/55)	49.09 (27/55)	47.27 (26/55)	81.13 (43/53)	9.4 (5/53)	49.05 (26/53)	43.39 (23/53)	52.38 (22/42)	47.61 (20/42)

Nodular heterotopias: 98.18% (54/55)														
Localization							Distribution		Number			Pattern		
	Periventricular													
	Lateral ventricle													
Subcortical	Body	Trigone	Frontal horn	Temporal horn	IV ventricle		Bilateral	Monolateral	Absent	<4	>4	Single	Confluent	Mixed
5.55 (3/54)	62.96 (34/54)	59.25 (32/54)	59.25 (32/54)	31.48 (17/54)	42.59 (23/54)	1.85 (1/54)	77.77 (42/54)	22.22 (12/54)	1.85 (1/55)	20.63 (13/63)	73.02 (46/63)	29.62 (16/54)	22.22 (12/54)	40.74 (22/54)

Results of the systematic review of MRI studies according to the classification proposed by Hopkins et al.[9]
[a] Cysts were classified according the Barkovich classification.[11]

Figure 1 Corpus Callosum (CC) Malformations



T1-weighted sagittal MRI shows complete (A) or partial (B, C) agenesis of the CC; absence of the posterior part of the body and of the splenium and rostrum (B) or only of the genu and the rostrum (C); and complete but diffusely hypoplastic CC (D).

Seizures Onset

Seizures onset occurred at a mean age of 75.45 days (2.5 months) (range 1–540 days). At onset, half of the patients presented with epileptic spasms, 38.81% displayed multiple seizure types, and only a minority of cases focal seizures. As regards seizure frequency, all the patients had multiple daily seizures. The results recorded on seizures are reported in table 2.

Evaluable electroencephalographic reports at seizure onset were available in 54/67 patients; in 48.15%, EEG was characterized by poor background activity with multifocal epileptiform discharges; 29.63% had a definite hypsarrhythmic pattern, while 22.22% had a suppression burst pattern. The severity of EEG abnormalities at onset was statistically correlated with the severity of the motor and language outcome. In particular, patients with a suppression burst pattern scored level V on the GMFCS and the MACS, and III–IV on the clinical language scale: GMFCS (KW 6.783, $p = 0.0337$), MACS (KW 7.315, $p = 0.0258$), and language scale (KW 7.143, $p = 0.0281$). Precisely, for the 3 scales, the median score was significantly higher in patients with suppression burst with respect to those with hypsarrhythmia ($p = 0.014$, $p = 0.010$, and $p = 0.011$, respectively).

Moreover, statistical analysis revealed a worse manual outcome in patients who presented focal seizures alone at onset; the median score was significantly higher in patients with focal seizures with respect to those with spasms at onset (KW 8.982, $p = 0.0112$).

Seizures Follow-up

During a mean follow-up of 123.05 months (range 9–324 months), the majority of the cases (79.68%) displayed multiple seizure types, while a few cases presented only epileptic spasms or focal seizures alone. Status epilepticus was reported in 20.31% of cases. At the last evaluation, only one patient was seizure-free (at the age of 5 years); the other developed drug-resistant epilepsy. Among those in whom accurate seizure frequency evaluation data were available (54 cases), 57.41% displayed multiple daily seizures, 31.48% had weekly seizures (1–7 seizures/week), and 9.26% had ≤4 seizures/month. Over the years, most of the patients tried more than 3 antiepileptic drugs; in 1 case, as many as 17. Parents and clinicians reported a reduction in seizure frequency with vigabatrin, ACTH, valproic acid, and lamotrigine. Five patients tried a ketogenic diet without obtaining clear results in terms of

Table 2 Seizure Type and Frequency, n (%)

	Seizure onset	Seizure follow-up
Seizure type		
Spasms	34/67 (50.75)	4/64 (6.25)
Focal seizures	7/67 (10.45)	7/64 (10.94)
GTCS		2/64 (3.12)
Multiple types of seizures	26/67 (38.81)	51/64 (79.68)
Spasms + focal seizures	22/26	23/51
Spasms + GTCS	2/26	1/51
Spasms + focal seizures + GTCS	0/26	8/51
Myoclonic seizures + other types of seizures	1/26	6/51
SE + other types of seizures	1/26	13/51
Seizure frequency		
Multiple daily seizures	67/67 (100)	31/54 (57.41)
Weekly seizures (1–7 seizures/week)		17/54 (31.48)
≤4 Seizures/month		5/54 (9.26)
Seizure-free		1/54 (1.85)

Abbreviations: GTCS = generalized tonic-clonic seizures; SE = status epilepticus.

efficacy. Statistical analysis showed correlations between poorer seizure control and both neurologic outcome as evaluated using the clinical neurologic scoring system (KW 9.753, $p = 0.0076$) and manual abilities (KW 9.058, $p = 0.0285$): more than 50% of the patients with multiple daily seizures scored level V on the MACS.

Neurologic Outcome

Developmental milestones were delayed in 98.50% of patients; 2 of these patients presented only language delay. As regards their neurologic outcome (available for 62 cases), at the last evaluation, 46.77% had severe spastic tetraplegia, 12.90% severe diffuse hypotonia, and 35.48% hemiplegia or diplegia; 2 patients showed slight pyramidal signs; in 21 patients extrapyramidal signs, specifically dystonia and dyskinesia, were reported; only 1 patient had a normal neurologic examination, at 5 years of age.

With regard to motor functions, in most of the patients (66.66%) the ability to maintain antigravity control was severely limited and they needed a wheelchair (GMFCS levels V and IV). However, 26.19% of the cases required wheeled mobility only for long distances, being able to walk shorter distances with assistive devices (levels III and II); only 4 patients were independent walkers, with minimal balance or coordination problems (level I). A total of 67.24% of the cases had limited or no ability to handle objects, while 31.03% had some residual ability to handle objects, albeit with some difficulty; just one patient showed little impairment of manual abilities and partial independence in daily activities. Language was absent or consisted of simple vocalizations or babbling in 80.95%; 11.1% of the patients could utter a few words, and only 5 patients could speak in simple sentences. Feeding problems were frequently reported (74%) with different degrees of severity. The results and percentage distribution recorded on the clinical outcome scales are reported in table 3.

Comorbidities

In subsets of the cohort, available medical history data allowed us to establish the presence of comorbidities. Scoliosis was found in 70% of 40 patients, associated in 27.5% with vertebral dysmorphisms (fused or cleft vertebræ, hemi or butterfly vertebræ). Recurrent respiratory infections were documented (57.14%, out 35 cases), particularly pneumonia. Sleep problems, awakenings, or sleep apnea were reported in 19 out 35 patients in whom data were available; 22 presented behavioral problems, stereotypic hand movements, or aggressivity.

Neuroradiologic Results

Imaging was performed at a median age of 45 months (range: first day of life–235 months). Table 1 details the results of the systematic review of the neuroradiologic images.

CC Dysgenesis

CC malformations were found in 100% of the patients, while absence of the posterior part of the body and splenium and rostrum was predominant in patients with partial agenesis (71.42%) (figure 1). Callosal dysgenesis was directly correlated with the clinical neurologic scale (KW 6.551, $p = 0.0378$; the median score was significantly higher in patients with complete callosal agenesis with respect to patients with CC hypoplasia, $p = 0.015$), and with the GMFCS (KW 7.128, $p = 0.0283$) and MACS (KW 7.244, $p = 0.0267$); higher scores on all these clinical outcome scales were found in patients with complete agenesis.

Intracranial Cysts

Cysts were present in 96.36% of the 55 patients whose MRI studies were reviewed. In most cases these were uniloculated (81.13%), interhemispheric supratentorial (61.19%) cysts; almost half showed ≥2 cysts; 33.33% had choroid plexus cysts or papillomas. On classifying the cysts according to Barkovich,[11] we found similar rates of type 2b (hyperintense-to-CSF signal on T1-weighted images) and type 2d (CSF-like signal, as in arachnoid cysts) (figure 2).

Cortical Abnormalities

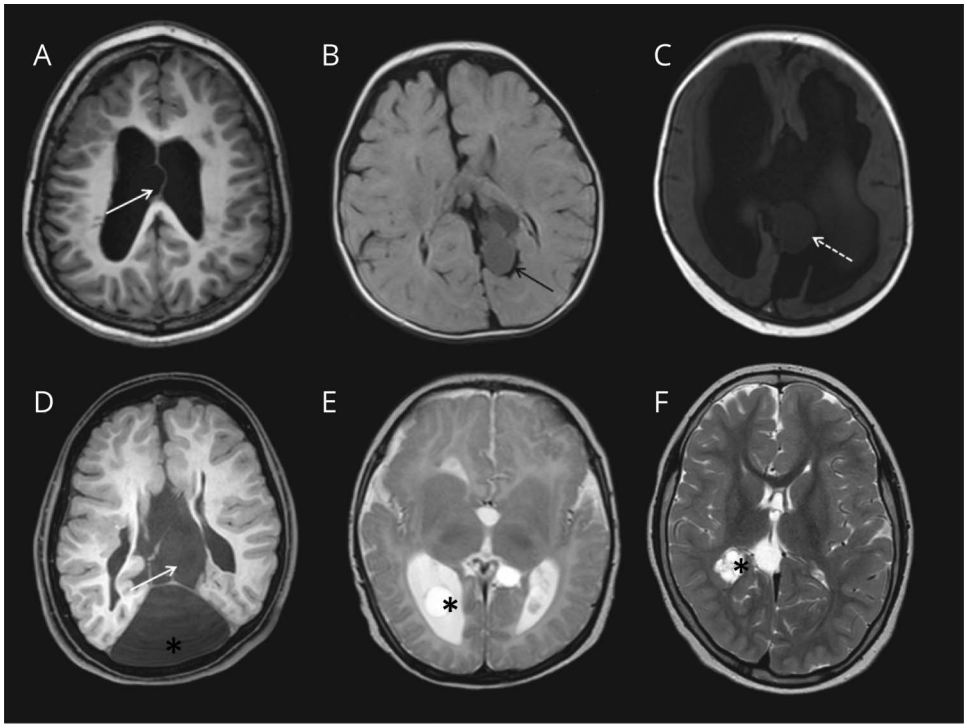
The available images and reports were clear enough to allow systematic description of abnormal cortical involvement in 64/67 patients: 87.5% displayed diffuse bilateral or multifocal cortical dysplasia, while only 10.94% had focal dysplasia. In the 55 patients whose images have been reviewed, the dysplasia showed a polymicrogyria-like pattern in 72.22% of cases. In 3 cases, polymicrogyria was associated with schizencephaly. In 72.22%, an anterior–posterior gradient of the cortical malformation was identified, particularly involving the

Table 3 Clinical Outcome Scale Results

	I	II	III	IV	V	Total n
GMFCS	4 (6.3)	8 (12.69)	9 (14.28)	9 (14.28)	33 (52.38)	63
MACS	1 (1.72)	7 (12.06)	11 (18.96)	10 (17.24)	29 (50)	58
EDACS	13 (26)	5 (10)	7 (14)	8 (16)	17 (34)	50
language	5 (7.9)	7 (11.1)	9 (14.28)	13 (20.63)	29 (46.03)	63

Abbreviations: EDACS = Eating and Drinking Ability Classification System; GMFCS = Gross Motor Function Classification System–Expanded and Revised; MACS = Manual Ability Classification.
Language classification scale: ability to say sentences (class 0), ability to say single words (class 1), babbling (class 2), vocalization (class 3), none of the aforementioned (class 4). Values are n (%).

Figure 2 Cysts



T1-weighted axial images (A, D) show single unilocular interhemispheric supratentorial arachnoid cysts (white arrow), with CSF-like signal (type 2d according to the Barcovich classification); in (D), associated with an infratentorial arachnoid cyst (*). T1-weighted axial images (B, C) show multilocular (black arrow, B) and unilocular (dashed white arrow, C) supratentorial interhemispheric cysts with hyperintense to CSF signal (type 2b according to the Barcovich classification), probably glioependymal cysts. T2-weighted axial images (E, F) show choroid plexus cysts (asterisk, E) and papillomas (asterisk, F).

frontal, opercular, and sylvian cortex (figure 3). In 40.74%, we observed asymmetric distribution of the dysplastic cortex, while 54.54% of the cases showed gross cerebral hemisphere volume asymmetry. Hippocampal dysmorphisms (vertical or stubby looking) were detected in 94.54% of the patients. Our analysis revealed a significant association between cortical malformations and the presence of seizures at onset ($p = 0.032$); cortical malformations were also associated with higher scores on all the clinical outcome scales: more than 50% of the patients with a diffuse bilateral abnormal cortical pattern scored level V on the GMFCS, MACS, and EDACS, and level IV (the most severe) on the clinical neurologic and language scales: GMFCS (KW 17.031, $p = 0.0007$), MACS (KW 12.912, $p = 0.0048$), EDACS (KW 14.121, $p = 0.0027$), language scale (KW 10.521, $p = 0.0146$), and neurologic scale (KW 9.609, $p = 0.0222$). For GMFCS, MACS, EDACS, and language scales, the median score was significantly higher in patients with diffuse with respect to multifocal polymicrogyria ($p < 0.001$, $p = 0.0035$, $p = 0.0030$, and $p = 0.0043$, respectively). In addition, a significant correlation was found between abnormal cortical pattern and EEG at onset (χ^2 13.805, df 4, $p = 0.005$).

Nodular Heterotopias

Of the 55 patients whose brain scans were reviewed, 98.18% presented heterotopias. According to the anatomical distribution, periventricular heterotopias were observed mostly around lateral ventricles and mainly involved anterior portions, less frequently the occipital and temporal horns. In 3 cases, subcortical nodules were associated. Most of the cases had more than 4 nodules with a bilateral or asymmetric distribution (most frequently both patterns) (figure 3). The number of nodular heterotopias was statistically correlated with GMFCS (KW 6.972, $p = 0.0306$; the median score was significantly higher in patients with >4 nodules of heterotopias with respect to patients with <4 nodules, $p = 0.0145$): ≥50% of patients with more than 4 nodules scored level V.

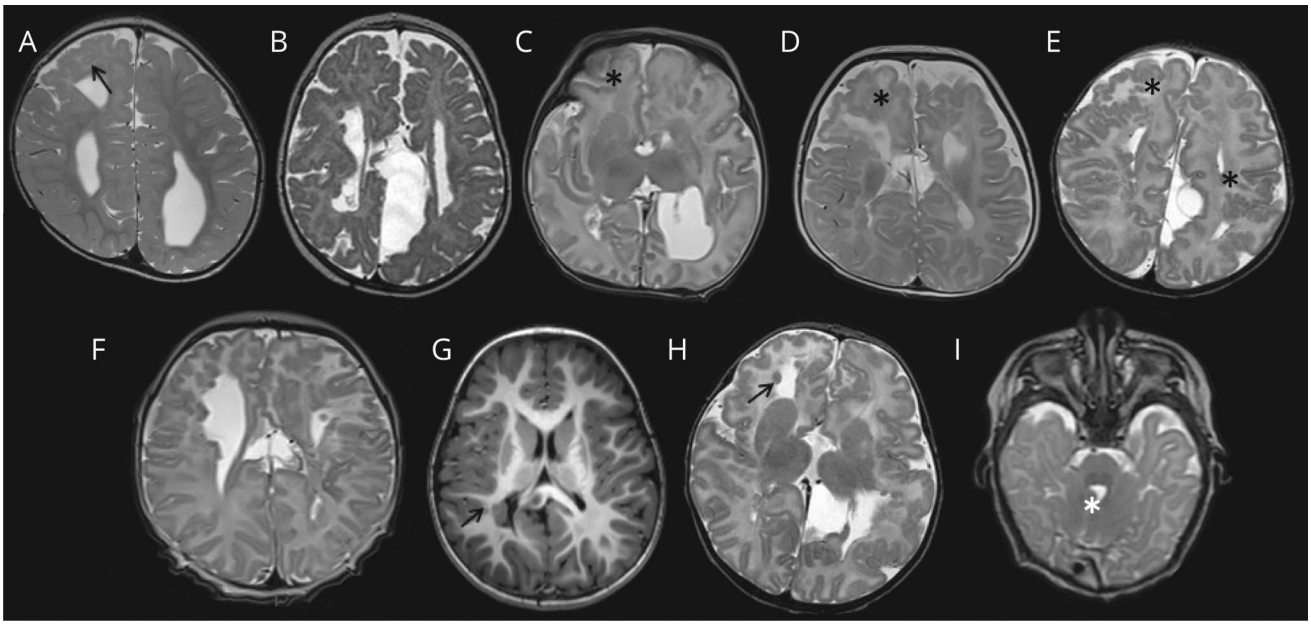
Posterior Fossa Malformations

In 63.63% of the 66 patients, posterior fossa malformations were detected; among these, 2/3 of the cases had mild abnormalities (in particular vermis hypoplasia or vermian rotation associated in 42.85% with an enlarged cistern magna), while 1/3 showed complex posterior fossa malformations, ranging from severe cerebellar hypoplasia (12/14) predominantly associated with cerebellar cortical dysplasia (8/10) to (less frequently) rhombencephalosynapsis (2/14), Dandy-Walker continuum (1/14), and brainstem hypoplasia (1/14) (figure 4).

Basal Ganglia Dysmorphisms

In 76.36% of patients, MRI also revealed basal ganglia dysmorphisms, both mild and severe. The milder forms were characterized by a stubby and globular appearance or slight hypoplasia of the striatum, often associated with a straight but finely jagged lateral profile of the putamen. The more severe ones (47.61%) were associated with hypertrophic thalamic adhesion (11.90%) or internal capsule anterior limb agenesis (35.71%). Among this latter group, 9 patients also had

Figure 3 Cortical Malformations



Cortical dysplasia: T2-weighted axial images show different distributions of cortical dysplasia: focal (arrow, A), multifocal (C, D, E), and diffuse (B), in most cases with a polymicrogyric pattern (asterisk, C, D, E), mostly with an anterior-to-posterior gradient (C, D). Nodular heterotopias: T2-weighted axial images (F, H, I) and inversion recovery T1 axial image (G) show the presence of periventricular heterotopias. The nodules could be numerous and spread asymmetrically around the lateral ventricles (F), and could be single (arrow, H), confluent (arrow, G), or both (F). A single case of subependymal heterotopia of the IV ventricle was detected (asterisk, I).

microcysts along the straight jagged profile of the putamen, likely small dilated perivascular spaces, more evident on one side (figure 4). In these 9 cases, radiologic evidence of internal capsule anterior limb agenesis prompted genetic screening of the tubulin genes, which was found to be negative.

Other MRI Features

With regard to the ventricular system, 61.81% of the 55 reviewed patients had ventriculomegaly, which was asymmetric in 6 cases. In 89.09%, ventricular dysmorphisms were detected, with a range of features including the colpocephalic appearance typically associated with CC agenesis, or more complex patterns with focal enlargements of the ventricular system or indentation deformities due to nodular heterotopias or to choroid plexus cysts.

No white matter abnormalities were observed, except for hyperintense or blurred subcortical white matter signals, probably associated with cortical malformation.

Finally, coloboma was detected on MRI/CT in 32/55 patients, bilaterally in 12; in 22/48 (45.83%), the optic nerves and chiasm were assessed, and asymmetric thinning was found in half of the cases.

In all cases, the pituitary gland was well recognizable both in adeno- and neuro-hypophyseal portions, and showed a regular morphology.

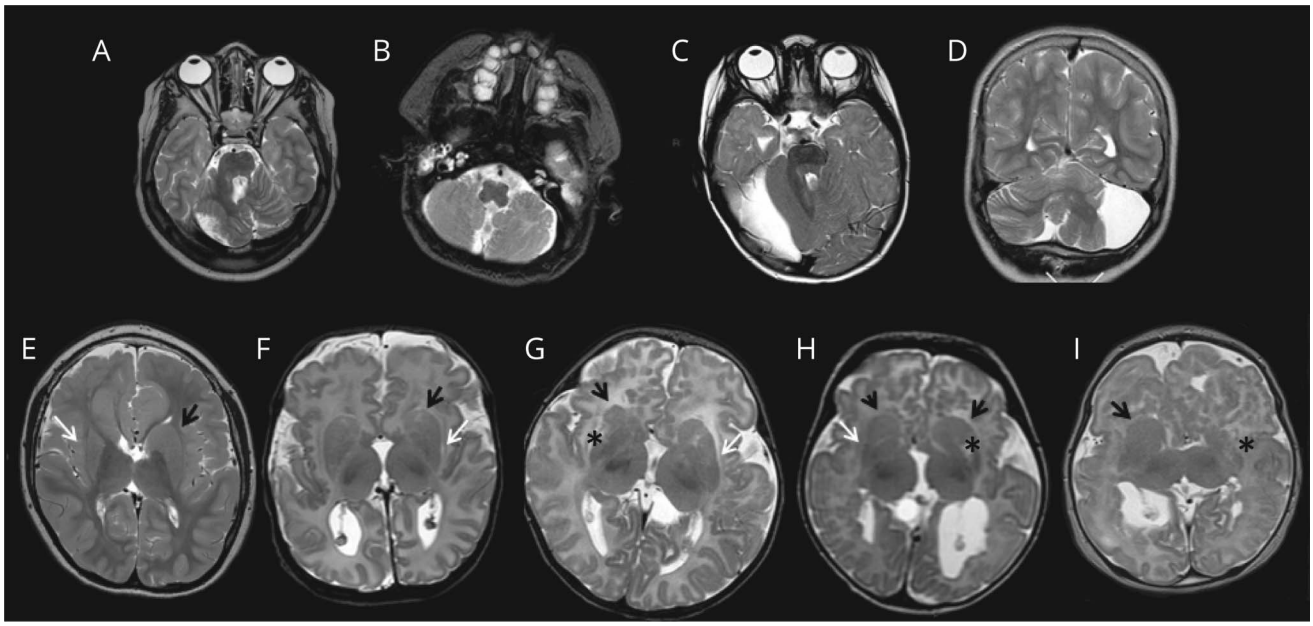
Discussion

AIC is a rare sporadic congenital condition.[4] In line with the literature,[12] all of our patients displayed an early-onset epilepsy, mostly with spasms, with a severe EEG derangement in half of them. The majority subsequently developed drug-resistant epilepsy, displaying different types of seizures, including a high rate of status epilepticus. Most of our patients presented chorioretinal lacunae, confirming that these are a pathognomonic sign that should prompt clinicians to consider this diagnosis. Patients with AIC are usually severely neurologically disabled[5,13,14]; nevertheless, a few cases with a favorable outcome have been reported.[15,16] Confirming this, in our sample, the use of objective methods of evaluation allowed us to detect several residual capacities: the possibility of handling objects, walking, and some independence in daily activities. Language was found to be more impaired than motor functions.

The first aim of our study was to detect associations between neuroradiologic features and EEG traces/clinical–neurologic outcomes. The statistical analysis supported the presence of such associations. The large cohort described, which was the most extensive to date statistically evaluated in AIC, with a wide range of clinical presentations, and the standardized clinical scales used, give more value to the present study.

First, we detected a direct correlation, previously only hypothesized,[17] between CC agenesis and motor impairments

Figure 4 Posterior Fossa and Basal Ganglia Dysmorphisms



Posterior fossa dysmorphisms: T2-weighted axial (A, B, C) and coronal (D) MRI show (A) complex posterior fossa malformation with rhomboencephalosynapsis and hemispheric schizencephaly, (B) left cerebellar cortical dysplasia and inferior vermis hypoplasia, and (C) right cerebellar cortical dysplasia and fusion with the vermis, likely representing incomplete rhomboencephalosynapsis. (D) Cortical dysplasia of the right cerebellar hemisphere (left and superior aspects) and vermis. Basal ganglia dysmorphisms: T2-weighted axial images show a stubby and globular appearance or slight hypoplasia of the striatum with an irregular and straight lateral profile of the putamen (white arrow, E, F, G, H), variably associated with microcysts along the irregular profile of the putamen (asterisk, G, H, I)—likely small dilated perivascular spaces—and internal capsule anterior limb agenesis (black arrow, E ,F, G, H). (I) Association with thalamic adhesion can also be observed.

(both gross motor functions and manual abilities). However, CC agenesis cannot be the only factor responsible for the clinical outcome. Romaniello et al.,[18] in a cohort of 162 patients with CC agenesis, observed more severe neuromotor deficits in syndromic and nonsyndromic cases with associated cerebral malformations than in nonsyndromic cases with isolated CC agenesis. In our sample, most of the patients with complete agenesis had severe polymicrogyria and a higher number of heterotopic nodules, features that might explain their worse scores on outcome scales. A diffuse abnormal cortical pattern was statistically associated with higher scores on all the clinical outcome scales: GMFCS, MACS, the neurologic and language scales. Moreover, the number of nodular heterotopias was directly related to the severity of outcome as assessed using the GMFCS. Interestingly, cortical malformations were also found to be related to long-term feeding problems, EEG, and seizures at onset. Our results corroborate the first hypothesis advanced by Aicardi,[12] which considered cortical dysplasia the main determinant of mental retardation, seizures, and neurologic signs. No correlation was found between posterior fossa dysmorphisms and clinical outcome, despite the possible influence of the cerebellum and brainstem on language profile.[18] In addition, we found that EEG at onset correlated with worse motor functions and language scales and can be considered a further prognostic factor, as previously only hypothesized.[6,19,20] Neidich et al.,[21] in a small cohort, observed a relationship between drug resistance and severity of developmental delay; in the same way, in our study, seizure outcome was correlated with neurologic and motor outcome. Our observations are in line with the well-known effects of encephalopathic changes on motor functions and cognition, which depend on the efficacy of seizure control.[22]

In parallel, our careful review of the neuroradiologic images allowed us to characterize all the brain malformations observed in AIC. Callosal dysgenesis, mostly presenting as agenesis, was a constant feature. We confirm that cysts (mainly interhemispheric supratentorial) are a typical finding in AIC; we found a slight prevalence of 2b vs 2d ones, in line with the hypothesis advanced by Aicardi[12] and corroborated in further studies.[9,13] The cortex is usually extensively involved, with the exception of a few patients showing single areas of dysplasia. As previously observed by Hopkins et al.,[9] an anterior–posterior gradient of severity of the cortical dysplasia was found in most of our patients. Heterotopic nodules were almost universally present: multiple, asymmetric, with a periventricular and a predominantly anterior location. Considering both our sample and that of Hopkins et al.,[9] we can speculate that this anterior–posterior gradient (a typical characteristic of both the cortical dysplasia and the heterotopias) might constitute a cortical pattern specific to AIC. We also confirm the high frequency of posterior fossa abnormalities.[9]

Moreover, our imaging review brought to light basal ganglia dysmorphisms as a new, unexpected, and previously

unreported MRI feature. Frequently observed in our sample, these ranged from mild to more severe forms, associated with hypertrophic thalamic adhesion or agenesis of the anterior limbs of the internal capsulae. Both milder and more severe forms were characterized by a similar stubby and globular appearance of the basal nuclei, associated with a straight, finely jagged profile of the putamen; moreover, most of the patients with internal capsule anterior limb agenesis had associated microcysts along the basal profile of the putamen, interpreted as small dilated perivascular spaces. Taking into account the high prevalence of these latter dysmorphisms in our sample, we suggest that they might conceivably be considered as a new additional feature of the complex brain malformation in AIC. Basal ganglia dysmorphisms should not be considered pathognomonic but as a new feature over the well-known ones, which should be recognized with their importance as the others in delineating the complex brain malformation of the syndrome, which might assist the etiologic pathway. Interestingly, in most of our patients with the most severe basal ganglia dysmorphisms, genetic analysis excluded tubulinopathies.[23] Karyotype analysis,[3] investigation of candidate genes (*FLNA, TEAD1, OCEL1*),[24–26] methylation array,[27] and, more recently, advanced genetic analysis in the form of exome sequencing,[23] carried out by different research groups, have thus far failed to solve the genetic puzzle of AIC. The severe and diffuse involvement of multiple brain structures observed in our large cohort resembles the broad spectrum of findings in tubulinopathies. The commissure is commonly involved in these latter conditions, and it is possible to observe gyration abnormalities with different degrees of cortical involvement. Moreover, common findings are heterotopias, hippocampal abnormalities, posterior fossa abnormalities, and the rather characteristic involvement of deep gray nuclei. Oculomotor nerve and optic nerve involvement have also been reported.[28] Our study demonstrates a similar disruption of multiple brain structures in patients with AIC.

On the basis of these findings, we speculate that elusive, possibly unconventional, mutations may affect genes encoding for microtubule-associated proteins or other microstructures of cytoskeleton, whose integrity and functions are essential in driving cell proliferation and migration. This hypothesis is supported by the occurrence of filamin inclusions in astrocytes of patients with AIC and may hold the key to "the mystery of AIC."[24,29]

Our study, which presents the most extensive neuroradiologic sample of AIC reviewed to date, highlights the imaging complexity of this condition, which is being found to involve an increasing number of brain structures. Our study documents the concomitant presence of multiple brain malformations; indeed, the well-known CC dysgenesis, associated with polymicrogyria, nodular heterotopias, and intracranial cysts, was found to be frequently associated with posterior fossa abnormalities and a previously unreported feature: basal ganglia dysmorphisms. All this adds up to a complex brain malformation that only recognized in its entirety should be considered as a peculiar aspect of AIC and examined in the diagnostic workup of the disease; it should also be considered one of the important early prognostic factors that can help predict the long-term clinical outcome.

Future studies in larger cohorts and, possibly, the identification of the genetic etiology will likely provide critical insights into the complex phenotypic spectrum of AIC.

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Disclosure

S. Masnada, A. Pichiecchio, M. Formica, F. Arrigoni, P. Borrelli, P. Accorsi, P. Bonanni, R. Borgatti, B. Dalla Bernardina, A. Danieli, F. Darra, and N. Deconinck report no relevant disclosures. V. De Giorgis received speaker fees from Eisai. O. Dulac, S. Gataullina, L. Giordano, and R. Guerrini report no relevant disclosures. F. La Briola received speaker fees from Italfarmaco. M. Mastrangelo, M. Montomoli, M. Mortilla, E. Osanni, and P. Parisi report no relevant disclosures. E. Perucca received speaker and/or consultancy fees from Amicus Therapeutics, Arvelle, Biogen, Eisai, GW Pharma, Intas Pharmaceuticals, Sanofi, SunPharma, Takeda, UCB Pharma, and Xenon Pharma. L. Pinelli, R. Romaniello, M. Severino, and F. Vigevano report no relevant disclosures. A. Vignoli received speaker and/or consultancy fees from Eisai, GW Pharma, Italfarmaco, and Sanofi. N. Bahi-Buisson, M. Cavallin, A. Accogli, M. Burgeois, V. Capra, V. Chaves-Vischer, L. Chiapparini, G. Colafati, S. D'Arrigo, I. Desguerre, M. Doco-Fenzy, G. d'Orsi, N. Epitashvili, E. Fazzi, A. Ferretti, E. Fiorini, M. Fradin, C. Fusco, T. Granata, K.M. Johannesen, S. Lebon, P. Loget, R.S. Moller, D. Montanaro, S. Orcesi, C. Quelin, E. Rebessi, A. Romeo, R. Solazzi, C. Spagnoli, C. Uebler, and F. Zara report no relevant disclosures. A. Arzimanoglou received speaker and/or consultancy fees and/or educational grants from Arvelle, Eisai, GW Pharma, Takeda, UCB Pharma, and Caixa Foundation. P. Veggiotti received speaker fees from Eisai, Nutricia, Dr. Schar, and Pediatrica. Go to Neurology.org/N for full disclosures.

Publication History

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Appendix *(continued)*

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Continued

Appendix *(continued)*

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Appendix *(continued)*

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Appendix *(continued)*

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Appendix *(continued)*

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Katrine Marie Johannesen, MD, PhD	Department of Epilepsy Genetics and Personalized Treatment, The Danish Epilepsy Centre, Dianalund; Institute for Regional Health Services, University of Southern Denmark, Odense	Member of the Aicardi Syndrome International Study Group; provided clinical, EEG, and neuroradiologic data of the cases; reviewed the manuscript.

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Appendix *(continued)*

Name	Location	Contribution
Sebastien Lebon, MD	Unit of Pediatric Neurology and Pediatric Neurorehabilitation, Woman-Mother-Child Department, Lausanne University Hospital CHUV, Switzerland	Member of the Aicardi Syndrome International Study Group; involved in the care of the patients described in this article; provided clinical, EEG, and neuroradiologic data of the cases; reviewed the manuscript
Philippe Loget, MD	Service de Genetique Clinique, CLAD-Ouest, Hospital Sud, Rennes, France	Member of the Aicardi Syndrome International Study Group; involved in the care of the patients described in this article; provided clinical, EEG, and neuroradiologic data of the cases; reviewed the manuscript
Rikke Steensbjerre Moller, MD, PhD	Department of Epilepsy Genetics and Personalized Treatment, The Danish Epilepsy Centre, Dianalund; Institute for Regional Health Services, University of Southern Denmark, Odense	Member of the Aicardi Syndrome International Study Group; provided clinical, EEG, and neuroradiologic data of the cases; reviewed the manuscript
Domenico Montanaro, MD	Unit of Neuroradiology, Fondazione CNR/ Regione Toscana G. Monasterio, Pisa, Italy	Member of the Aicardi Syndrome International Study Group, performed and provided MRI examinations of the patients described in this article, reviewed the manuscript.
Simona Orcesi, MD	Department of Brain and Behavioural Neurosciences, University of Pavia; Child Neurology and Psychiatry Unit, IRCCS Mondino Foundation, Pavia, Italy	Member of the Aicardi Syndrome International Study Group; involved in the care of the patients described in this article; provided clinical, EEG, and neuroradiologic data of the cases; reviewed the manuscript
Chloe Quelin, MD	Service de Genetique Clinique, CLAD-Ouest, Hospital Sud, Rennes, France	Member of the Aicardi Syndrome International Study Group; involved in the care of the patients described in this article; provided clinical, EEG, and neuroradiologic data of the cases; reviewed the manuscript
Erika Rebessi, MD	Pediatric Neurology Unit and Epilepsy Center, Fatebenefratelli Hospital, Milan, Italy	Member of the Aicardi Syndrome International Study Group; involved in the care of the patients described in this article; provided clinical, EEG, and neuroradiologic data of the cases; reviewed the manuscript

Appendix *(continued)*

Name	Location	Contribution
Antonino Romeo, MD	Pediatric Neurology Unit and Epilepsy Center, Fatebenefratelli Hospital, Milan, Italy	Member of the Aicardi Syndrome International Study Group; involved in the care of the patients described in this article; provided clinical, EEG, and neuroradiologic data of the cases; reviewed the manuscript
Roberta Solazzi, MD	Department of Pediatric Neuroscience, Fondazione IRCCS Istituto Neurologico Carlo Besta, Member of the ERN EpiCARE, Milan, Italy	Member of the Aicardi Syndrome International Study Group; involved in the care of the patients described in this article; provided clinical, EEG, and neuroradiologic data of the cases; reviewed the manuscript
Carlotta Spagnoli, MD	Child Neurology Unit, Pediatric Department, Azienda USL-IRCCS di Reggio Emilia, Italy	Member of the Aicardi Syndrome International Study Group; involved in the care of the patients described in this article; provided clinical, EEG, and neuroradiologic data of the cases; reviewed the manuscript
Christian Uebler, MD	KJF Klinik Josefinumg GmbH, Klinikfür Kinder und Jugendliche, Neuropädiatrie, Augsburg, Germany	Member of the Aicardi Syndrome International Study Group; involved in the care of the patients described in this article; provided clinical, EEG, and neuroradiologic data of the cases; reviewed the manuscript
Federico Zara, MD, PhD	Pediatric Neurology and Muscular Diseases Unit, Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa; Laboratory of Neurogenetics and Neuroscience, IRCCS Istituto Giannina Gaslini, Genoa, Italy	Member of the Aicardi Syndrome International Study Group, involved in the Aicardi collaboration study, reviewed the manuscript
Alexis Arzimanoglou, MD, PhD	Department of Paediatric Clinical Epileptology, Sleep Disorders and Functional Neurology, University Hospitals of Lyon, Coordinator of the ERN EpiCARE, Lyon, France; Pediatric Epilepsy Unit, Child Neurology Department, Hospital San Juan de Dios, Member of the ERN EpiCARE and Universitat de Barcelona, Spain	Involved in the care of the patients described in this article; provided clinical, EEG, and neuroradiologic data of the cases; was involved in the Aicardi collaboration study; followed the process of preparing the manuscript up to each final version

Appendix *(continued)*

Name	Location	Contribution
Pierangelo Veggiotti, MD	Department of Child Neurology, V. Buzzi Children's Hospital, and Department of Biomedical and Clinical Sciences, L. Sacco, University of Milan, Italy	Involved in the care of the patients described in this article; provided clinical, EEG, and neuroradiologic data of the cases; was involved in the Aicardi collaboration study; followed the process of preparing the manuscript up to each final version

References

1. Sutton VR, Hopkins BJ, Eble TN, et al. Facial and physical features of Aicardi syndrome: infants to teenagers. Am J Med Genet A 2005;138A:254–258.
2. Aicardi J, Lefebvre J, Lerique-Koechlin A. A new syndrome: spasms in flexion, callosal, agenesis, ocular abnormalities. Electroencephalogr Clin Neurophysiol 1965;19:609–610.
3. Donnenfeld AE, Packer RJ, Zackai EH, Chee CM, Sellinger B, Emanuel BS. Clinical, cytogenetic, and pedigree findings in 18 cases of Aicardi syndrome. Am J Med Genet 1989;32:461–467.
4. Aicardi J, Chevrie JJ, Rousselie F. [Spasma-in-flexion syndrome, callosal agenesis, chorioretinal abnormalities.] Arch Fr Pediatr 1969;26:1103–1120.
5. Rosser TL, Acosta MT, Packer RJ. Aicardi syndrome: spectrum of disease and long-term prognosis in 77 females. Pediatr Neurol 2002;27:343–346.
6. Grosso S, Lasorella G, Russo A, et al. Aicardi syndrome with favorable outcome: case report and review. Brain Dev 2007;29:443–446.
7. Iturralde D, Meyerle CB, Yannuzzi LA. Aicardi syndrome: chorioretinal lacunae without corpus callosum agenesis. Retina 2006;26:977–978.
8. Paulson A, Vargus-Adams J. Overview of four functional classification systems commonly used in cerebral palsy. Children 2017;4.
9. Hopkins B, Reid Sutton V, Lewis RA, et al. Neuroimaging aspects of Aicardi syndrome. Am J Med Genet A 2008;146A:2871–2878.
10. Masnada S, Chiara D, Giana I, et al. Aicardi syndrome: key fetal MRI features and prenatal differential diagnosis. Neuropediatrics 2020;51:276–285.
11. Barkovich AJ, Simon EM, Walsh CA. Callosal agenesis with cyst: a better understanding and new classification. Neurology 2001;56:220–227.
12. Aicardi J. Aicardi syndrome. Brain Dev 2005;27:164–171.
13. Uccella S, Accogli A, Tortora D, et al. Dissecting the neurological phenotype in children with callosal agenesis, interhemispheric cysts and malformations of cortical development. J Neurol 2019;266:1167–1181.
14. Menezes AV, MacGregor DL, Buncic JR. Aicardi syndrome: natural history and possible predictors of severity. Pediatr Neurol 1994;11:313–318.
15. Lee SW, Kim KS, Cho SM, Joo Lee S. An atypical case of Aicardi syndrome with favorable outcome. Korean J Ophthalmol 2004;18:79–83.
16. Abe K, Mitsudome A, Ogata H, Ohfu M, Takakusaki M. A case of Aicardi syndrome with moderate psychomotor retardation. No To Hattatsu 1990;22:376–380.
17. Hamano S, Yagishita S, Kawakami M, Ito F, Maekawa K. Aicardi syndrome: postmortem findings. Pediatr Neurol 1989;5:259–261.
18. Romaniello R, Marelli S, Giorda R, et al. Clinical characterization, genetics, and long-term follow-up of a large cohort of patients with agenesis of the corpus callosum. J Child Neurol 2017;32:60–71.
19. Prats Vinas JM, Jesús Martinez Gonzalez M, Garcia Ribes A et al. Callosal agenesis, chorioretinal lacunae, absence of infantile spasms, and normal development: Aicardi syndrome without epilepsy? Dev Med Child Neurol 2005;47:419–420; discussion 364.
20. Ohtsuka Y, Oka E, Terasaki T, Ohtahara S. Aicardi syndrome: a longitudinal clinical and electroencephalographic study. Epilepsia 1993;34:627–634.
21. Neidich JA, Nussbaum RL, Packer RJ, Emanuel BS, Puck JM. Heterogeneity of clinical severity and molecular lesions in Aicardi syndrome. J Pediatr 1990;116:911–917.
22. Pindrik J, Hoang N, Smith L, et al. Preoperative evaluation and surgical management of infants and toddlers with drug-resistant epilepsy. Neurosurg Focus 2018;45:E3.
23. Lund C, Striano P, Sørmo Sorte H, et al. Exome sequencing fails to identify the genetic cause of Aicardi syndrome. Mol Syndromol 2016;7:234–238.
24. Van den Veyver IB, Panichkul PP, Antalffy BA, et al.. Presence of filamin in the astrocytic inclusions of Aicardi syndrome. Pediatr Neurol 2004;30:7–15.
25. Schrauwen I, Szelinger S, Siniard AL, et al. A de novo mutation in TEAD1 causes non-X-linked Aicardi syndrome. Invest Ophthalmol Vis Sci 2015;56:3896–3904.
26. Wong BK, Sutton VR, Lewis RA, Van den Veyver IB. Independent variant analysis of TEAD1 and OCEL1 in 38 Aicardi syndrome patients. Mol Genet Genomic Med 2017;5:117–121.
27. Piras IS, Mills G, Llaci L, et al. Exploring genome-wide DNA methylation patterns in Aicardi syndrome. Epigenomics 2017;9:1373–1386.
28. Goncalves FG, de Andrade L Freddi T, Taranath A, et al. Tubulinopathies. Top Magn Reson Imaging 2018;27:395–408.
29. Wong BKY, Sutton VR. Aicardi syndrome, an unsolved mystery: review of diagnostic features, previous attempts, and future opportunities for genetic examination. Am J Med Genet C 2018;178:423–431.