Aicardi Syndrome

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Synonyms and related keywords: callosal agenesis, ocular abnormalities, syndrome of spasm-in-flexion, Aicardi's syndrome, brain malformations, agenesis of the corpus callosum, dysmorphic facies, cleft lip, cleft palate, seizure, e infantile spasm, mental retardation, hemivertebrae, fused vertebrae, rib abnormalities, scoliosis, chorioretinal lacuna pathognomonic lesions, retinal colobomata

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Disclosure

INTRODUCTION

Background: In 1965, a French neurologist, Dr Jean Dennis Aicardi, described 8 children with infantile spasm-in-flexion, agenesis of the corpus callosum, and variable ocular abnormalities. clinical scenario, already reported in 1949, was recognized as an entity distinct from congenita infections. An additional 7 patients were described in 1969, and, in 1972, Dennis and Bower established the Aicardi syndrome designation.

Further patient study demonstrated other less consistent characteristics outside the classic tria findings. These additional characteristics include abnormal facies, cleft lip and palate, and vert body abnormalities. Most children have a moderate-to-severe degree of mental retardation, alt less severely affected children occasionally are described. To date, only 1 affected child has b male.

Pathophysiology: At present, no etiology explains all the manifestations of Aicardi syndrome. Findings are ascribed to neural tube overdistension during embryogenesis at 4-8 weeks' gesta experimental evidence is lacking, and the cause remains unknown.

Frequency:

- **Internationally:** Although cases occur throughout the world, exact incidence and prevale unknown. In a series of children with infantile spasm, 2% had Aicardi syndrome. Given th phenotypic heterogeneity and diagnostic difficulties associated with young children, Aica syndrome may be a more frequent cause of mental retardation and seizure in girls than previously thought.

Mortality/Morbidity: Aicardi syndrome is often complicated by severe mental retardation, intra epilepsy, and a resultant propensity to pulmonary complications. The condition often leads to d the first decade. Sudden, unexplained death is common.

Race: The syndrome occurs in people of diverse racial backgrounds throughout the world with noted racial predominance.

Sex: Aicardi syndrome is thought to be an X-linked dominant disorder lethal to males. Except f single patient, all reported instances have been in females.

Age: Because Aicardi is a congenital syndrome, it is often first recognized during the neonatal and infancy. Less severely affected individuals may live into childhood and adolescence, and diagnosis may be delayed. In one group of patients, diagnosis was delayed from 11-234 week the onset of seizures.

CLINICAL

History:

- Aicardi syndrome is often diagnosed in female infants only after the onset of seizures or the presence of dysmorphic facies prompts further evaluation.
- If only visual abnormalities or developmental delays are present, the condition may not b recognized until the onset of seizures or if ophthalmologic evaluations demonstrate chara chorioretinal lacunae.
- Seizures are a common initial manifestation, most frequently infantile spasm. Chevrie et reported 97% of patients had infantile spasm, and the majority of these had seizures whe younger than 3 months. Additional seizure types noted include hemiconvulsions, comple seizures, and focal motor seizures.
- Electroencephalogram (EEG) findings are not consistent. In the relevant clinical scenario suppression pattern arising independently from each hemisphere suggests Aicardi syndr
- Global developmental delay is uniform, and most patients have moderate-to-severe men retardation. This characteristic is probably due to the combination of brain dysgenesis ar intractable epilepsy, although some children may walk and, in rare cases, develop expre language.
- Most of these children are unable to walk and are bedridden. Children with Aicardi syndr typically lack even rudimentary abilities to interact with their environments.
- Ocular abnormalities limit visual ability, blinding most children. Certain malignancies occu frequently, including embryonic soft tissue carcinoma, hepatoblastoma, and angiosarcon

Physical:

- Ocular
  - Pathognomonic lesions, called chorioretinal lacunae, commonly cluster around the disc of the eye and are described as punched-out, white- or yellow-colored defects lesions characteristically lack pigment, a characteristic that helps to distinguish thei lesions seen in infectious chorioretinitis. Classic chorioretinal lacunae do not enlarg progress. Although other ocular lesions exist in Aicardi syndrome, this manifestatio required for diagnosis.
  - Other common ocular lesions include the following:
    - Microphthalmos
    - Retrobulbar cyst
    - Cataract
    - Coloboma

        - Retinal detachment
        - Iris synechiae
- Craniofacial
    - Microcephaly, hemifacial asymmetry, microphthalmia, or plagiocephaly may be pre
    - Cleft lip and palate also occur with increased frequency.
- Musculoskeletal
    - Skeletal malformations are common but are not uniform in all patients.
    - Costovertebral abnormalities, such as hemivertebrae, fused vertebrae, and rib abnormalities, may be present.
    - Scoliosis resulting from these deformities can be disfiguring and disabling.
- Neurodevelopmental
    - Patients typically have profound mental retardation; however, the disease course n a milder expression in some than was thought historically.
    - Some children may walk and speak, though rarely. One of the few studies to exam natural history indicates that 21% of patients could ambulate, and 29% could comn These abilities appeared independent of seizure frequency, EEG findings, or other features studied during the first year of life.
    - If present, hypotonia, spasticity, or hemiplegia may complicate gross motor develo

Causes:

- Causes of various clinical manifestations are unknown.
- Events early in gestation, probably in weeks 4-8, are suspected causes. The exact etiolo these events remains elusive, although considerations have included in utero exposure t mild hypoxia, and infections. Investigation of these potential etiologies has been unrevea
- A genetic basis for the syndrome is favored, specifically an X-linked dominant mutation v lethality in male hemizygotes. Spontaneous mutation is most likely because siblings app spared, but parental gonadal mosaicism could be the basis for a reported pair of sisters v condition.
- The only male patient has been described with an XXY genotype.
- Skewed X chromosome inactivation may account for some clinical heterogeneity. Skewi increased in more severely affected patients.

Chorioretinitis

Other Problems to be Considered:

Infantile spasm
Developmental delay
Mental retardation
Agenesis of the corpus callosum

Lab Studies:

- If the clinical scenario is convincing, extensive laboratory studies are not indicated.
    - Most children should have high-resolution karyotyping. If the diagnosis is doubtful, metabolic error and congenital infection.
    - If typical clinical findings manifest in a male, look for an XXY chromosomal pattern.
    - Children with partial manifestations may have translocations that can influence repr

Imaging Studies:

- Neuroimaging can delineate the degree of CNS dysgenesis and help evaluate other pote epilepsy and developmental delay.
- MRI is preferred because its anatomic resolution is superior to CT scanning. Although C typical pattern of complete agenesis of the corpus callosum, partial agenesis and cortica not be evident.
- CT scanning can demonstrate calcifications (possible in congenital infections) better thar questionable, CT scanning may be a helpful additional study.
- Plain radiographs can help confirm the diagnosis by showing skeletal malformations. The costovertebral abnormalities, commonly affecting the thoracic vertebrae.

Other Tests:

- Ophthalmologic: Evaluation by an experienced ophthalmologist is crucial, especially if op chamber abnormalities) makes the examination more difficult.

- Electroencephalographic
    - Abnormalities are common.
    - Most patients suffer from multiple types of seizures, but EEG findings are inconsist
    - A pattern highly suggestive of the diagnosis in the typical clinical context is the pres pattern arising independently from each hemisphere. In one case, the EEG prompt characteristics to establish the diagnosis.
    - EEG findings, along with diminished seizure frequency, commonly evolve as a pati findings have shown an evolution from epileptic encephalopathy with suppression-l West syndrome and, subsequently, to the Lennox-Gastaut syndrome.

Histologic Findings: Multiple brain malformations are common and may include complete or callosum, cortical heterotopias, gyral malformation, and intraventricular cysts. These abnormal uniformly, and the brain's appearance may be grossly normal, with a preserved corpus callosu the parenchyma commonly reveals disordered cellular organization and disruption of the norm cortex.

Chorioretinal lacunae are described as well-circumscribed, punched-out lesions in the retinal p choroid. The region of these abnormalities contains severely disrupted retinal architecture; all vessel number and caliber are decreased, and pigmentary ectopia and pigmentary epithelial h

TREATMENT

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Medical Care:

- Seizures
    - Use conventional epilepsy therapies for the many possible seizure manifestations.
    - Infantile spasm requires specific interventions and typically is unresponsive to conv seizure type may be especially recalcitrant to therapy.
        - Adrenocorticotropic hormone (ACTH) is effective for some patients and shoul
        - Vigabatrin, a more recently introduced therapy for infantile spasm, blocks gar (GABA)–T, an enzyme that breaks down GABA, the major inhibitory neurotra concerns have been raised about possible ophthalmologic sequelae (eg, con after using vigabatrin, it has been effective for infantile spasm without the seri effects of ACTH. If retinal disruption from the congenital insult is deemed suff nature and sequelae of infantile spasm may outweigh the risks of using vigab medication is not currently approved for use in the United States, which precl
- Pulmonary

- Profound mental retardation, immobilization, seizures, and scoliosis may contribute dysfunction.
- Patients have a shortened life span and commonly die from pulmonary infections.
- Aggressive pulmonary toilet and alternate feeding routes (eg, feeding tubes) may h deterioration.

Consultations:

- Consultation with a child neurologist is probably needed during the first year of life.
- A pediatric ophthalmologist is best able to confirm retinal lacunae.
- If the diagnosis is doubtful, or if subsequent children are planned, a geneticist with exper helpful.
- Consult a cardiac, pulmonary, or gastroenterologic specialist if complications arise from s or feeding or aspiration difficulties.

Diet:

- No specific dietary recommendations exist.
- Use of the ketogenic diet to control seizures associated with this condition is not docume

Multiple medications are now available to treat infantile spasm, the most common initial epilep syndrome. Consider vigabatrin, although not FDA-approved, because of this disorder's ocular successful use in other conditions that have infantile spasm as a major manifestation. Vigabat the United States and cannot be considered the drug of choice. Initiate a detailed discussion w about the multiple medications available and the potential complications of each. Individualize patient and the capabilities and wishes of the family.

Drug Category: *Anticonvulsant agents* -- Effective management requires a detailed and a seizure types.

Drug Name	Corticotropin (ACTH, Acthar) -- Precise mechanism for infantile spasms unknown. Theorized that ACTH suppresses corticotropin-releasing hormone (CRH), which is an excitatory neuropeptide. Infants with infantile spasms may have increased CRH.
Adult Dose	40-80 U IM/SC qd/qod
Pediatric Dose	20-40 U/d IM or 80 U IM qod for 3 mo or 1 mo after seizures cease
Contraindications	Documented hypersensitivity; osteoporosis; ocular herpes simplex; recent surgery; systemic fungal infections; scleroderma; CHF

Interactions	May decrease effects of aspirin, indomethacin, and insulin; diuretics increase effects
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Use lowest possible dose and reduce gradually if a decrease in dose desired; adrenocortical insufficiency may persist for months after discontinuing therapy (reinitiate corticosteroid therapy in any situation of stress); do not administer live attenuated viral or bacterial vaccines to individuals receiving immunosuppressive doses of corticotropin
Drug Name	Vigabatrin (Sabril) -- Currently not approved by FDA, and benefits of successful treatment of infantile spasm must be weighed against potentially serious ophthalmologic complications. May be obtained as an orphan drug from Aventis Pharmaceuticals for infantile spasm. Synthetic derivative of GABA.
Adult Dose	2-3 g/d PO qd or divided bid; initiate at low doses and gradually titrate upward
Pediatric Dose	50-150 mg/kg/d PO has been used for infantile spasm
Contraindications	Documented hypersensitivity
Interactions	Lowers phenytoin levels by 15-30%; may increase carbamazepine levels
Pregnancy	D - Unsafe in pregnancy
Precautions	Closely monitor visual fields in patients able to comply with testing; discontinue drug (withdraw must be gradual) if visual symptoms occur (ie, concentric and predominantly nasal visual field constriction with temporal sparing); drowsiness is the most common adverse effect; psychotic effects (eg, hallucination, paranoia) or increased seizure activity may occur with abrupt initiation or withdrawal

FOLLOW-UP

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Complications:

- Early sudden death is typical and is usually caused by pulmonary complications such as
- Seizures or their treatments (eg, ACTH) may also be associated with increased morbidity infections) and death.
- The aforementioned malignancies may occur, and choroid plexus papillomas may cause

Prognosis:

- Prognosis is uniformly poor, with most children unable to walk or communicate; those wh and require continuous care for their needs.

- Children commonly die in the first decade of life, although some have lived into the secor

Patient Education:

- For excellent patient education resources, visit eMedicine's Brain and Nervous System C Children's Health Center. Also, see eMedicine's patient education articles Epilepsy and S

MISCELLANEOUS S
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Medical/Legal Pitfalls:

- To date, no evidence exists of an exogenous prenatal event that would explain this cond
- Because of reports of affected siblings, discuss recurrence risk with the family.

PICTURES Sc
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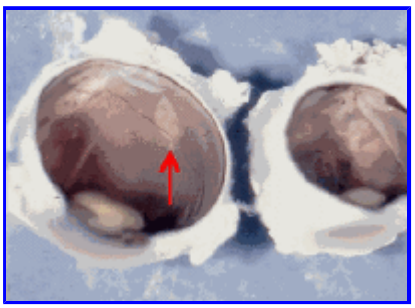
Caption: Picture 1. Cross-section of an eye in a patient with Aicardi syndrome. The arrow indicates chorioretinal lacunae.



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Picture Type: Photo

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