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# Aicardi syndrome and cognitive abilities: A report of five cases

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ABSTRACT

Aicardi syndrome is a rare neurodevelopmental disorder with agenesis of corpus callosum, chorioretinal lacunae, and infantile spasms as the main features. The outcome is in general severe, with poor cognitive development and difficult-to-treat epilepsy.

In this study, we assessed the level of cognitive function of five girls with Aicardi syndrome, using normed population based tests and questionnaires. Their cognitive abilities varied from mild to profound intellectual disabilities. The more severe the epilepsy, the poorer were the cognitive skills.

To the best of our knowledge, this is the first study that systematically applies validated cognitive assessment tools to study patients with this syndrome. Knowledge about cognitive functioning is crucial for providing optimal special education and finding appropriate alternative communication with parents and caregivers.



## 1. Introduction

Aicardi syndrome is a rare neurodevelopmental disorder, defined by Jean Aicardi in 1965 [1]. The main diagnostic features consist of a triad: agenesis of corpus callosum, chorioretinal lacunae, and infantile spasms. However, a diagnosis of Aicardi syndrome may also be made in cases with only two of these features if other typical findings in the brain, eyes, or skeleton are present [2].

Outcome is in general severe, with poor cognitive development and drug resistant epilepsy. The etiology is assumed to be genetic, but the exact genetic abnormality has not yet been discovered [3]. The syndrome is associated with a reduced life expectancy [3].

Recently, the original assumption that Aicardi syndrome is inevitably associated with severe developmental consequences has been challenged, as a few cases with a more favorable outcome have been reported [4–11]. "Favorable outcome" ranges from mild intellectual disabilities to apparently normal cognitive functioning. The cause of such a variation is not known, although different explanatory factors have been suggested; severity of the epilepsy [5] and extent of brain abnormalities [12]. Number and extent of ocular lesions are reported to be associated with a more severe cognitive outcome [13,14].

Evaluation of the cognitive outcome in Aicardi patients is difficult. Firstly, the syndrome is extremely rare, affecting only about 0.63 in 100,000 people [15]. Secondly, many of the patients are not able to carry out formal neuropsychological examination. In the largest study so far, Rosser and colleagues [2002] used questionnaire data collected from caregivers of 77 Aicardi patients from around the world. They found that 91% attained milestones corresponding to a 12 months old child, two patients had skills of a 2 years old child (6 years and 13 years at the time of reporting), and one girl had the skills of a 3 years old child (13 years at the time of reporting). In the same study, 21% were able to walk, and 12% were able to walk with minimal or no assistance. Three girls (4%) could speak in short sentences. The assessment of functioning was based on the parents' report of developmental milestones concerning gross and fine motor and language skills.

Currently we do not know how developmental trajectories unfold in patients with a more favorable outcome. Do they develop steadily forward or halt at a certain developmental level, or do they deteriorate later in life? Cognitive deterioration is evident in many patients with the syndrome, who are at the severe end of the spectrum. Does this hold true also for patients with a milder or apparently normal level of functioning? Neuropsychological testing, using standardized tests, is probably the best way to assess subtle changes and answering these questions.

The aim of the study was to provide further information about outcome and range of functioning, as well as discussing possible variables likely to affect outcome in these patients. Although this study does not hold the methodological power to discern the contribution of each of the various factors, a presentation of a case series like ours may add to the growing knowledge base of this extremely rare disease.

## 2. Patients and methods

### 2.1. Patients

By sending letters, including a description of diagnostic criteria of Aicardi syndrome to all departments of pediatrics, neurology,

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ophthalmology, radiology, neurosurgery, habilitation, and medical genetics in Norway, a total of six patients with Aicardi syndrome were identified [15], of which five took part in the cognitive assessment. The sample does not represent the complete population of Aicardi syndrome in Norway, as other cases have been identified since the conclusion of this study.

They were all assessed by the same neuropsychologist (MT). Four of the patients fulfilled all diagnostic criteria of Aicardi syndrome (agenesis of corpus callosum, chorioretinal lacunae and infantile spasms), while one did not have infantile spasms or other kinds of epileptic seizures. Nevertheless, the patient was considered to have the diagnosis as she, in addition to agenesis of corpus callosum and chorioretinal lacunae, had typical skeletal and other cerebral findings. The skeletal findings were scoliosis, 11 thoracic ribs, asymmetry of Th11, and cervical ribs at C7, and the cerebral findings were dilation of the lateral ventricles, cerebellar hypoplasia, possible frontoparietal microgyria, and possible cerebellar cortical dysplasia, in addition to agenesis of corpus callosum. This patient is described in detail by Matlary et al. [5]. The clinical characteristics of the five patients are described in Table 3 and by Lund et al. [15].

The Project was approved by the Regional Committee for Medical and Health Research Ethics of South Norway.

### 2.2. Methods

The neuropsychological tests were individually selected to match the cognitive level of the patient. Each girl was tested in her natural environment.

The estimation of the degree of intellectual disabilities was based on clinical observation; i.e. assessment of daily living skills, and where appropriate, scores on intelligence tests. Profound intellectual disabilities implies an IQ below 20 and a mental age below 3 years, moderate intellectual disabilities implies an IQ of 35–49, and mild intellectual disabilities implies an IQ of 50–69.

All five were screened using the Vineland Adaptive Behavior Scales, 2nd ed. (VABS II), Survey interview form [16] with parents.

The assessment of girls 1–3 (aged 12, 19 and 20 years, respectively) was based on the VABS II in addition to clinical observations.

Girl 4 (aged 6 years) was additionally assessed using the cognitive scale of Bayley Scales of Infant and Toddler Development, third edition (Bayley III) [17], parts of Wechsler Preschool and Primary Scale of Intelligence – Revised (WPSSI 3rd ed) [18], and parts of the visual-logical battery of Leiter International Performance Scale-Revised (Leiter-R) [19].

The assessment of girl 5 (aged 13 years) was based on the VABS II [16], as well as a full Wechsler Intelligence Scale for Children, 4th edition [20], selected tests from Leiter International Performance Scale-Revised [20] (Associative Memory and Delayed Associative Memory), selected tests from NEPSY [21] (Narrative Memory, Finger Discrimination, Manual Motor Sequences), The Beery-Buktenica Development Test of Visual-Motor Integration (VMI) [22], selected tests from Delis-Kaplan Executive Function System (D-KEFS) [23] (Verbal Fluency and Trail Making Test), motoric tests of side differences, a Norwegian verbal learning test [24], and the VABS II, Survey interview form [16] with parents.

To assess the level of intellectual disability, we used the Norwegian translated version of the diagnostic manual ICD-10 [25]. Beside the test results, we obtained supplementary information from caregivers and personnel at institutions who knew the patients well, along with observations of the patients in daily activities.

For girl 5 the IQ scores (verbal IQ, performance/visuospatial IQ and full scale IQ) were compared to a previous assessment performed 7 years earlier by a different clinician [5].

## 3. Results

A description of each girl's functional level is given in Tables 1 and 2.

Girls 1–3:
These girls had few responses in social communication. Girl 2 was reported to have a language of a few words at 5–6 years of age, but these were gradually lost. She showed no response to any visual stimuli and is most probably blind due to her eye abnormalities and encephalopathy. The other two girls showed signs of interest in visual stimuli and could focus their glance for a few seconds at the time. All three girls could to some degree communicate comfort or discomfort. Girl 2 was extremely sensitive on the left side of her body as she expressed discomfort while being touched on that side, and it was challenging to comb her hair and even brush her teeth on the left side. Thus, her parents and caregivers always sat on her right side when communicating with her by touching and speaking.
The girls were diagnosed with profound intellectual disabilities. Their motoric level of functioning was also severely affected; they all used a wheelchair and had gastric feeding tubes.

All three girls had a history of infantile spasms and hypsarrhythmia in EEG and had severe and refractory epilepsy later in life.

Girl 4:
The parents of this girl reported at the time of assessment (6 years) that she used up to three words herself, 5–10 different symbols as communication tools, and a few hand signs. She was also able to follow simple oral instructions. Her face- and body language was quite easy to interpret by caregivers and parents; she smiled and made “happy sounds” when happy, cried and showed resistance when she disliked something. She managed to match pictures with color and size, puzzles, and visually define and complete images with lacking information. She understood simple words and concepts, and she was interested in a picture book and stories being read to her. She had a left sided hemiplegia.
She was diagnosed with moderate intellectual disabilities. She too had a history of infantile spasms and hypsarrhythmia in EEG, but with increasing age she had fewer seizures and less epileptiform activity in EEG.
Girl 5:
She was at the age of 13 years diagnosed with mild intellectual disabilities, based on test results and observations. She obtained a

**Table 1**
Results from Vineland II Adaptive Behavior Scales, Survey interview form [16].

| Girl | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Diagnosis | Profound intellectual disabilities | Profound intellectual disabilities | Profound intellectual disabilities | Moderate intellectual disabilities | Mild intellectual disabilities |
| Average score adaptive behavior | Low | Low | Low | Low (close to moderate low) | Moderate low |
| Communication | Low | Low | Low | Low (close to moderate low) | Low |
| Daily living skills | Low | Low | Low | Low (close to moderate low) | Between adequate and moderate low |
| Socialization | Low | Low | Low | Low (close to moderate low) | Adequate |
| Motor skills | Low | Low | Low | Low (close to moderate low) | Adequate |

(Based on parents' ratings in Vineland-II Adaptive Behavior Scales, Survey interview form. Adequate is between −1 and 1 standard deviation from the mean, moderate low is between 1 and 2 standard deviations from the mean, and low is lower than 2 standard deviations from the mean).