Pediatric Neurology 52 (2015) 182–186

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

Aicardi Syndrome: An Epidemiologic and Clinical Study in Norway

Caroline Lund MD [a,*], Marit Bjørnvold MD, PhD [a], Mia Tuft MS [a], Hrisimir Kostov MD [b], Oddveig Røsby MD, PhD [c], Kaja K. Selmer MD, PhD [c]

[a] *National Centre for Rare Epilepsy-Related Disorders, Oslo University Hospital and the University of Oslo, Oslo, Norway*
[b] *National Centre for Epilepsy, Oslo University Hospital and the University of Oslo, Oslo, Norway*
[c] *Department of Medical Genetics, Oslo University Hospital and the University of Oslo, Oslo, Norway*

ABSTRACT

BACKGROUND: Aicardi syndrome is a rare neurodevelopmental disorder. The main diagnostic features are agenesis of corpus callosum, chorioretinal lacunae, and infantile spasms. The outcome is in general severe, with poor cognitive development and difficult-to-treat epilepsy. The aim of this study was to perform a nationwide epidemiologic survey of patients with Aicardi syndrome and describe their clinical features. Norway is a small country with a well-developed health system, making epidemiologic studies of rare diseases feasible and reliable. **METHODS:** We aimed at identifying all patients diagnosed with Aicardi syndrome in Norway. Prevalence of Aicardi syndrome was calculated for January 1, 2011. All available patients were examined, and their medical records were scrutinized. **RESULTS:** Six females aged 7 to 27 years with the diagnosis of Aicardi syndrome were identified. With a female population of 949,578 in ages 0 to 29 years, we found an age-adjusted prevalence of 0.63 per 100,000 females. One patient never had epileptic seizures. The other five had all experienced infantile spasms, all had at some point hypsarrhythmia in electroencephalography, two had a clear picture of suppression burst, whereas three had periods of suppression. Four of the five patients with seizure disorders experienced a marked improvement with time. **CONCLUSION:** We found an age-adjusted prevalence of 0.63 per 100,000 females with Aicardi syndrome and that their seizure disorder appeared to improve with age.

Keywords: Aicardi syndrome, rare disease, epilepsy, prevalence

Pediatr Neurol 2015; 52: 182-186

Introduction

In 1965, Jean Aicardi et al.[1] described a new entity characterized by a triad of features: agenesis of corpus callosum, ocular abnormalities, and spasms in flexion. In a larger series of patients, the syndrome was further delineated revealing ocular findings of chorioretinal lacunae as essential, frequent costovertebral anomalies and the near exclusive affection of the female gender.[2] Close to 50 years after the first description of Aicardi syndrome (OMIM 304050), the main diagnostic features are practically unchanged, although the improvement of modern imaging techniques have made important contributions.[3] Along with agenesis of corpus callosum, typical brain abnormalities include polymicrogyria, periventricular and subcortical heterotopia, intracranial cysts, cerebellar abnormalities, and enlarged cisterna magna.[4] A clear diagnosis of Aicardi syndrome is made in the presence of all three major criteria: agenesis of corpus callosum, chorioretinal lacunae, and infantile spasms. However, a diagnosis of Aicardi syndrome is also possible in the presence of only two of the main criteria if other typical findings in the brain, eyes, or skeleton are present.[3] Characteristic facial features of Aicardi syndrome have been described,[5] but these are subtle and too unspecific for diagnostic purposes.

The epilepsy of Aicardi syndrome has been characterized as severe and drug resistant in most cases. Typical early

Article History:
Received September 2, 2014; Accepted in final form October 26, 2014
* Communications should be addressed to: Dr. Lund; National Centre for Rare Epilepsy-Related Disorders; Oslo University Hospital and the University of Oslo; Pb. 853; 1306 Sandvika; Norway.
E-mail address: carolinebplund@hotmail.com

0887-8994/$ - see front matter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pediatrneurol.2014.10.022

electroencephalography (EEG) findings include evidence of asynchrony between the hemispheres, hypsarrhythmia, and burst suppression, but the reported prevalence of these findings in individuals with Aicardi syndrome has varied in previous studies.[1,6-10] The etiology of Aicardi syndrome is still unknown. However, as the disorder is only observed in females and in males with chromosome 47, XXY in healthy families, it is assumed to be caused by a *de novo* mutation on the X chromosome and inherited in a dominant manner with hemizygous lethality in males.[3]

Aicardi syndrome is a rare disorder associated with a reduced life expectancy. A previous study has estimated the incidence to be 1 per 93,000-167,000 live births.[11] However, epidemiologic data are scarce. Only one previous nationwide study exists.[12] We summarize a national epidemiologic survey and describe the clinical features of Aicardi syndrome in Norwegian patients.

Methods

To identify all patients with Aicardi syndrome, letters including a description of diagnostic criteria of Aicardi syndrome were sent to all departments of pediatrics, neurology, ophthalmology, radiology, neurosurgery, habilitation, and medical genetics in Norway. Announcements were made at professional meetings and in journals for Norwegian neurologists and pediatricians.

The National Centre for Epilepsy and the National Centre for Rare Epilepsy-Related Disorders provides care for patients with severe epilepsy. Registers and medical records in both these institutions were available to the authors.

After the patients were identified, all but one was examined by the same neurologist (C.L.) and the same psychologist (M.T.). Medical data from all relevant hospitals were collected. All patients with epilepsy had visited the National Centre for Epilepsy several times and had been carefully observed and monitored with EEG. EEGs were examined by the same neurophysiologist (H.K.). Only patients with chorioretinal lacunae and agenesis of corpus callosum were included.

Statistical information of the inhabitants in Norway and Sweden was obtained from Statistic Norway's Information Centre (Statistisk sentralbyrå, www.ssb.no) and Statistics Sweden (Statistiska centralbyrån, www.scb.se). Approval to conduct this study was granted by the Regional Ethical Committee (REK sør-øst). Written informed consent was obtained from all legal guardians of the patients in the study.

Results

Epidemiologic data

At the point prevalence day (January 1, 2011), there were six patients with the diagnosis of Aicardi syndrome in Norway. All were females aged 7 to 27 years (mean, 16.7 years). Individuals with Aicardi syndrome have a reduced life span. Thus, we have calculated an age-adjusted prevalence based on the number of inhabitants in Norway aged 0 to 29 years. Assuming that half of the population of 1,899,156 in this specific age group are female, the female population at prevalence date was 949,578. This gives an age-adjusted prevalence of 0.63 per 100,000 females. Five patients had all of the cardinal features: infantile spasms, agenesis of corpus callosum, and chorioretinal lacunae. One patient had neither epileptic seizures nor infantile spasms. Nevertheless, she had agenesis of corpus callosum, chorioretinal lacunae, and typical cerebral and skeletal findings.

Seizures, EEGs, and epilepsy treatment

EEG disclosed cerebral asynchrony in all six individuals, included the one without epilepsy. In the five patients with epilepsy, there were 10 to 30 (mean 22) EEG recordings available. Age of seizure onset was 6 to 14 weeks (mean, 10.4 weeks). Three patients first developed focal seizures followed by asymmetrical infantile spasms. In two patients, infantile spasms was the first seizure type. EEG demonstrated initial focal abnormalities in three and hypsarrhythmia in the other two. However, all developed hypsarrhythmia within the first 6 months after birth. The hypsarrhythmia was described as atypical in three and typical in two. Two patients had an EEG recording with suppression burst (at 2.5 and 8 years). The other three only had periods of suppression. Later, they all developed a multifocal epileptiform activity and multiple seizure types. These seizure types were atypical absences, focal seizures, tonic seizures, myoclonic seizures, and generalized tonic-clonic seizures. The epilepsy improved markedly in four of five patients at ages of 2 years, 12 years, and in the late teens and the early twenties, respectively. The oldest (27 years) and the youngest (6 years) of these patients now only rarely have seizures. The other two still have regular seizures, daily or weekly respectively, in spite of the improvement. One adult experienced only slight improvement of her epilepsy over the years. She still has daily seizures, in spite of having been treated with several antiepileptic drugs (AEDs), vagus nerve stimulation (VNS), and a ketogenic diet.

Those with epilepsy had been treated with 4 to 16 different AEDs (mean 9.8). All had tried a ketogenic diet and three had a VNS implanted. In retrospect, it has been difficult to assess the efficacy of the different treatments. One patient had no seizure reduction with VNS, which was explanted. The two other patients had a modest improvement with VNS.

Clinical data

Clinical findings are summarized in Table. Additionally, all patients are described in detail in the Supplementary data. All patients were intellectually disabled, although to a variable degree. There was a clear association between degree severity of epilepsy and psychomotor development. Patient 6 was exceptional as she did not have epilepsy, was only mildly intellectually disabled, had relatively good language function, and exhibited nearly normal motor function. Patient 1 had severe epilepsy as an infant, but her seizure disorder improved at age 2 years. At age 6 years, she is able to communicate without words and she is able to walk, although with a hemiplegic gait. The other four patients who experienced refractory epilepsy throughout their childhood are now all wheelchair bound, have no language, and have multiple disabilities.

Obvious dysmorphic features were unilateral microphthalmia in two patients, acquired microcephaly in two, and brachycephaly in three patients. Comparing the patients to the facial and physical features described by Sutton et al.,[5] we found a prominent premaxilla in four of five examined patients.