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THE AICARDI SYNDROME*
A Case report and review of the literature

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A case of Aicardi's syndrome is described. The main features described are infantile spasms, pathognomonic chorioretinal lacunar defects, agenesis of the corpus callosum, psychomotor retardation, female sex, characteristic EEG changes and costovertebral anomalies. This is the second reported case in Turkey. *Key words: Aicardi syndrome.*

The Aicardi syndrome was initially described by Aicardi et al[1] in 1965 as a syndrome characterized by infantile spasms, agenesis of the corpus callosum, specific chorioretinal lacunar defects and costovertebral anomalies. Since then, more than 100 cases have been reported. Many other congenital abnormalities have since been included in this syndrome such as Dandy-Walker malformation, hydrocephalus, papilloma of choroid plexus, cleft lip and palate, and absence of the pineal gland[2-5]. While this syndrome has so far been reported to occur only in females, there is one case with male phenotype and XXY karyotype in the literature[6].

This report presents a description of the second case in Turkey. The first was reported by Karagöl and Yalaz[7].

Case Report

A three-month-old girl with a history of seizures was admitted to our hospital. When she was 40 days old, myoclonic jerkings started five to six times per day. One month later, she began having seizures of the same frequency, beginning on

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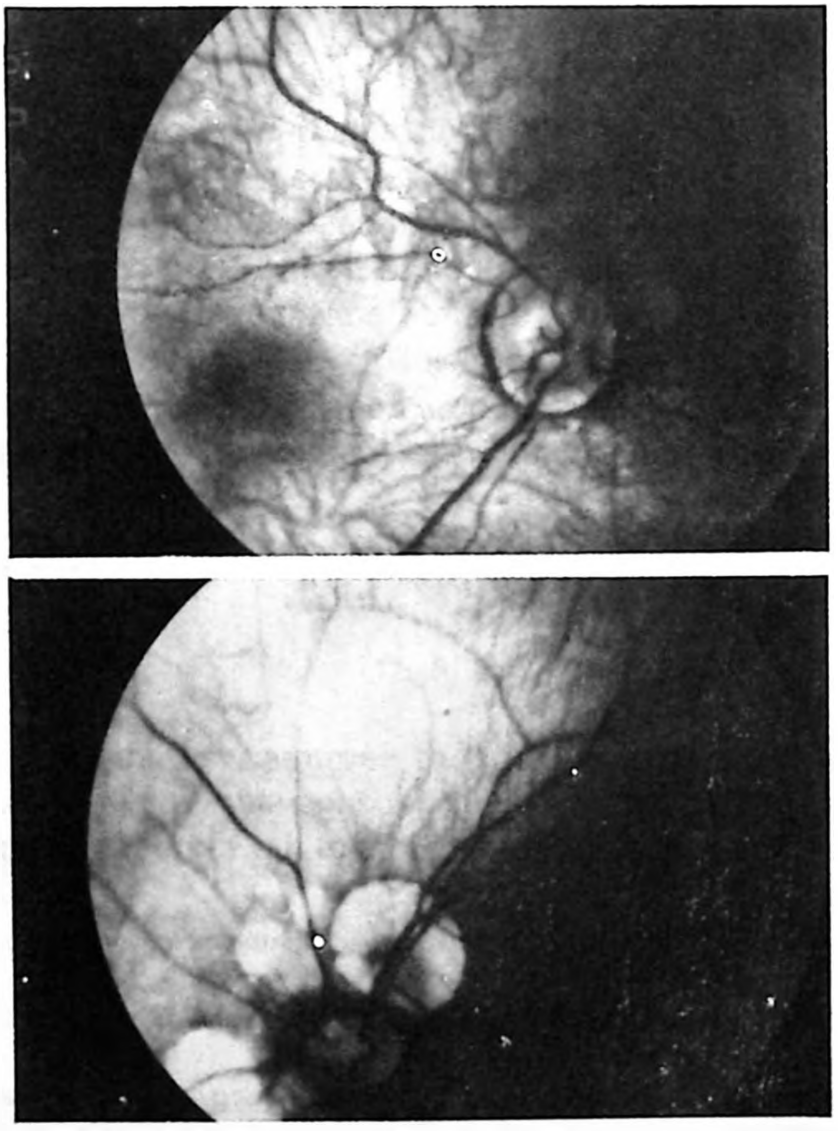
the right side of the body but sometimes becoming generalized. She was the first child of a 30-year-old, healthy mother and 32-year-old, healthy father. After an uncomplicated gestation, she was born at term by cesarean section, with a birth weight of 3200 g. No perinatal anoxia was described. There was no consanguinity.

On admission, the patient's weight was 5500 g (50th percentile), length was 60 cm (75th percentile), head circumference was 38 cm (20th percentile), and her vital signs were normal and stable. Circulatory and respiratory system and abdominal findings were normal. She had good sucking and Moro reflexes and good muscle tone. Deep muscle stretch reflexes were normal. She could not hold her head in an upright position. When she was in the prone position, she could not elevate her head. Her eyes did not follow light. An ophthalmological evaluation revealed ptosis and exotropia in the right eye; colobomatous optic discs which were smaller on the right, large and ovoid on the left; and chorioretinal lacunae and depigmented areas on the retinae (Figs. 1, 2).



Figs. 1, 2: Fundus photographs of the patient's right and left eyes showing colobomatous discs, irregularly shaped lacunae and hypopigmentation and hyperpigmentation areas near the discs.

Laboratory findings: complete blood count, serum glucose, urea, electrolytes, aminotransferase, calcium, phosphorus, ammonia, urine analysis, blood gas analysis, cerebrospinal fluid (CSF) examination, urine metabolic screening and amino acid chromatography of blood were normal. TORCH titers were negative. Chromosome analysis revealed 46, XX. Chest and spine radiographs were normal. Cranial computed tomography revealed cerebral atrophy and agenesis of the corpus callosum (Fig. 3). On her first electroencephalography (EEG), there was no abnormal discharge, and the background activity was relatively normal on the right side of the brain; on the left side, however, there were no sleep spindles and many high-amplitude sharp wave, poly spike and wave discharges which appeared in intervals of varying lengths and lasted 0.5-3 sec. along with irregular background activity (Fig. 4). These findings persisted despite intravenous infusion of 100 mg pyridoxine.

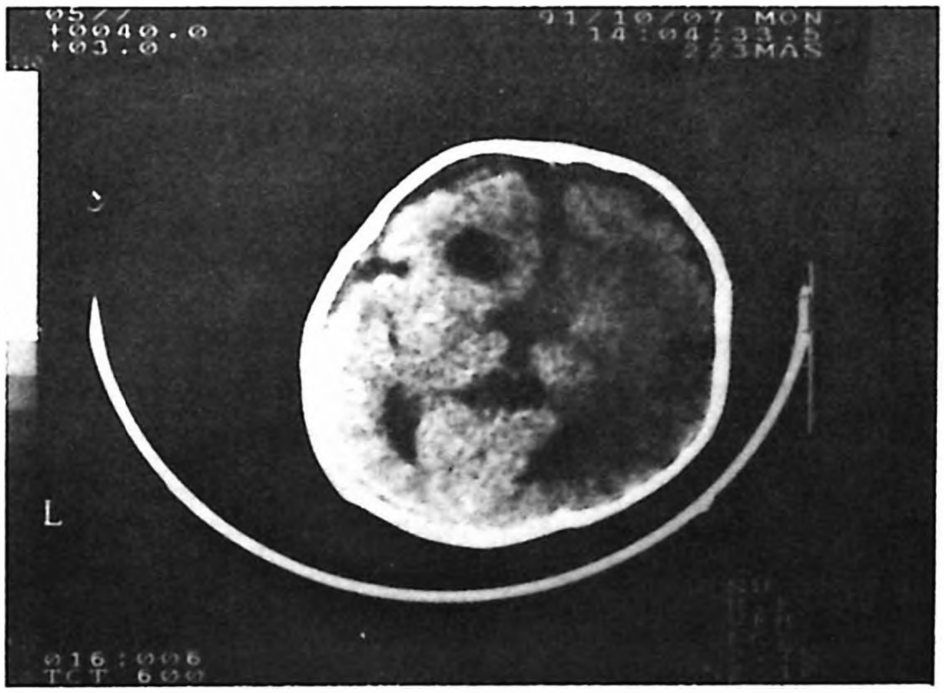


Fig. 3: Computerized tomographic scan of the patient showing cortical atrophy and agenesis of corpus callosum.

After admission to the hospital, the patient's secondary generalized seizures were controlled by oral phenobarbital at a dose of 5 mg/kg/day. Her myoclonic seizures were extensor in type (Fig. 5). For these myoclonic seizures, oral clonazepam was started at a dose of 0.05 mg/kg/day and gradually increased to 0.17 mg/kg/day. Clonazepam was then discontinued and valproic acid was given at an initial dose of 10 mg/kg/day, and gradually increased to 30 mg/kg/day. Administration of course of adrenocorticotropic hormone (ACTH) at a dose of 0.5 mg once per week intramuscularly was attempted twice. The first time was to be a 10

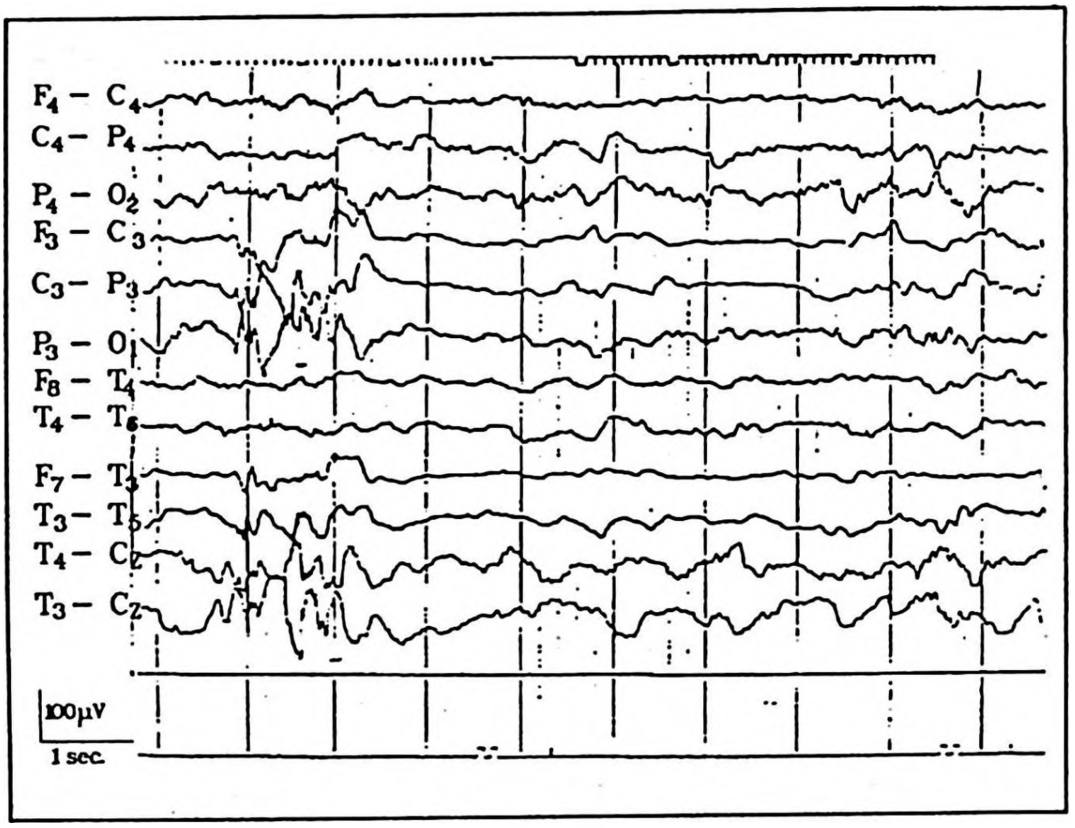


Fig. 4: The first EEG of the patient at 3 months of age showing normal right hemisphere, abnormal background activity and epileptiform discharges with irregular intervals and partial suppression periods on the left hemisphere.

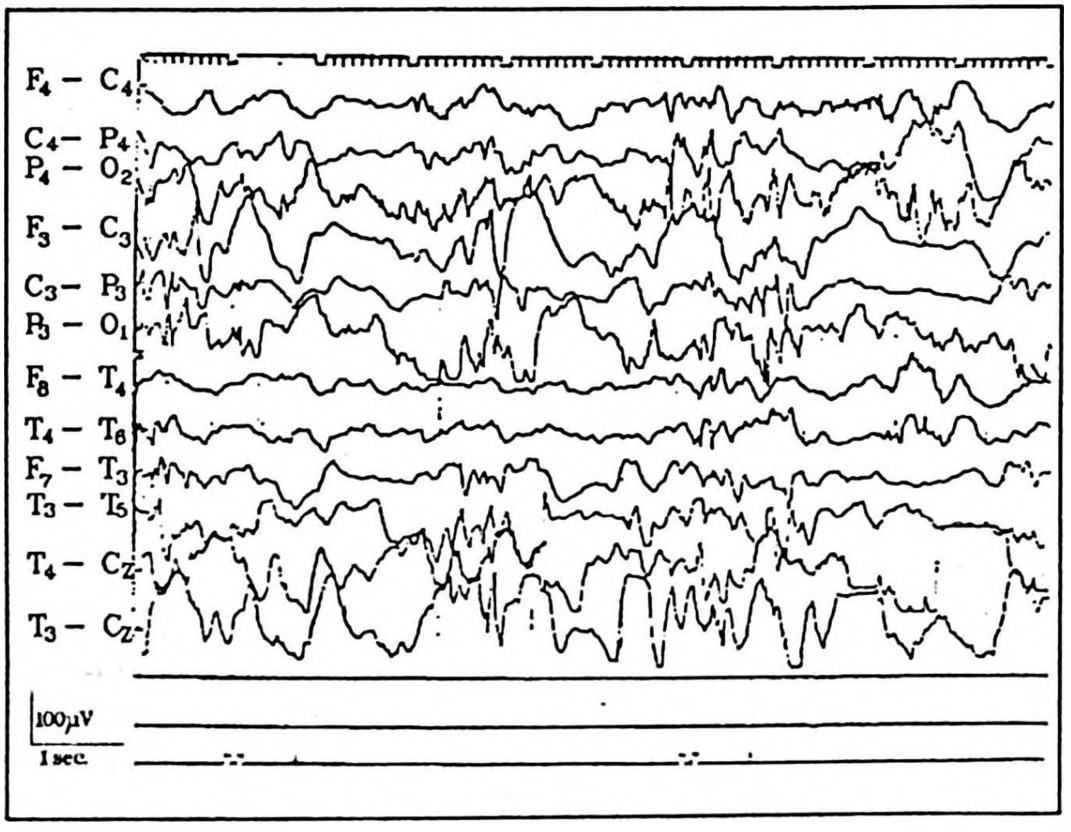


Fig. 5: An EEG obtained at 11th months showing abnormal discharges on the right hemisphere and increase of abnormal discharges and suppression periods on the left.

week course and the second a six week course, but both times it needed to be discontinued because of pulmonary infection. This medication provided only partial control of myoclonic seizures. Abnormal discharges on EEG, which were seen only on the left side at the beginning, appeared on the right side, though were less severe, when the patient was eight months old. The asymmetry of sleep spindles, irregularity of background activity, abnormal discharges and suppression periods were continuous. However, abnormal discharges increased, sleep spindles on the right decreased, background activity became more irregular and multiple spike activity appeared when the patient was 11 months old.

Discussion

Our patient had the characteristic features of this syndrome as described by Aicardi[1,8], such as female sex, infantile spasms, mental subnormality, specific EEG abnormalities, agenesis of the corpus callosum and chorioretinal lacunar defects, but did not have costovertebral anomalies. Aicardi et al[8] reported that chorioretinal defects were diagnostic for this syndrome.

The etiologic origin of the syndrome has been debated since the original description. The commisural plate, which develops from the commisura anterior, is formed in the fetus between the fourth and seventh weeks of gestation. The corpus callosum is formed by intussusception during the third month. The retinal pigment appears in the fourth week and the choroidal pigment in the fifth; the papilla also closes during the fifth week. The pathogenetic agent, either exogenous or endogenous, should work at this time or earlier[4]. Although early intrauterine insults by exogenous agents can lead to severe developmental anomalies, the tests for infective and toxic agents have been negative[9]. Aicardi et al[8] reported that this syndrome is most-likely inherited as an X-linked dominant trait with lethality in the male hemizygote. This is a rare mode of inheritance but has been described in several human diseases[10,11]. The occurrence of this syndrome exclusively in females, with exception of one male with 47, XXY karyotype, is very suggestive of an X-linked mutational event. Occurrence in a single dizygotic twin[12] confirms this concept. A balanced de novo X/3 translocation was detected in one patient, suggesting that the affected gene is located on the short arm of the X chromosome[11]. Until Moline et al[13] described two cases in sisters, not twins, the offspring of healthy parents, this syndrome was described in six sets of twins, five dizygous and one unspecified[14], and the occurrence of more than one case in the some family was not reported. This fact supported the concept of X-chromosome mutation. The occurrence of two cases in the same family with normal phenotypic mother[13] decreased the possibility of X-linked dominant inheritence of the disorder. A germinal mutation in one of the X-chromosomes of either the father or the mother may explain these two cases in the same family. In a study done to detect an X-chromosome inactivation pattern

in peripheral lymphocytes from seven patients with Aicardi syndrome, Neidich et al[15] reported the absence of a random X-inactivation pattern; however, some exhibited a skewed X-inactivation pattern, suggesting the occurrence of an X-linked locus. Again, in this study no deletion in X-chromosome was detected.

Aicardi et al[8] reported that the average age of onset of seizures was 1.8 months with range of one day to 4 months; the age of onset of flexor spasm ranged from one to five months. The onset of myoclonic jerking in our patient was at the age of 40 days, while focal seizures started at the age of two months. Myoclonic seizures, generally reported in the literature as flexor in type, were extensor in type in our patient. But there are several cases with extensor spasms reported in the literature[13]. Other than myoclonic, the seizure type was usually focal in the original series of Aicardi[8,16], as it was in our case. It was reported that the frequency of seizures and the severity of psychomotor retardion varied from case to case[15]. The seizures were usually refractory to therapy, as in our case. Intractibility of epileptic seizures, the type of EEG abnormalities, and severe mental retardation are related to cortical heterotopias, and they are never present in children with isolated agenesis of the corpus callosum[16]. The lacunae vary in size from 0.1 mm to several disc diameters and have a sharply demarcated "punched out" appearance (Fig. 1, 2). The other reported eye findings included microphthalmia, hypopigmented and hyperpigmented areas on the retina, persistent pupillary membrane, iris synechiae, staphyloma and glial tissue on the disc and retina[16-18]. Many other congenital anomalies have been described in numerous cases. These include ventricular dilatation, Dandy-Walker malformation, cerebral and cerebellar atrophy, papilloma of the choroid plexus, microgyria, lissencephaly, cleft lip and palate, costovertebral dysplasias, segmentation and fusion of vertebrae, absence of dorsal vertebrae and dorsal portion of ribs, hemivertebrae, scoliosis, plagiocephaly, syndactyly and other bone abnormalities[16,19].

Fariello et al[16] reviewed 32 EEGs from six cases of Aicardi syndrome and reported that there was a characteristic EEG pattern in all cases which included multifocal epileptiform anomaly, burst- suppressions, and asynchronous activity in the two hemispheres as if coming from different brains; after six months the EEG pattern included multifocal epileptiform discharges over a quite irregular background activity, no normal electrophysiologic sleep activity such as sleep spindle, vertex sharp wave and K-complex. They suggested that these characteristic EEG features are important clues in the diagnosis of Aicardi syndrome. When our patient was three-months old, there was irregular background activity without sleep spindle, abnormal discharges coming with irregular intervals consisting of sharp wave, spike and wave, and polyspike and wave which lasted 0.5-1 sec, after which partial suppression periods were seen in the left hemisphere; however, the

right hemisphere displayed normal background activity and sleep spindles and no abnormal discharge. On the EEGs in the 6th, 7th, 8th and 10th months, irregular background activity, independent activity of the two hemispheres and suppression periods persisted. During therapy with ACTH, abnormal discharges decreased. But after discontinuing this medication, abnormal discharges were also seen in the right hemisphere and increased in the left. Dennis and Bower[20] reported two important features of EEG in a case of Aicardi syndrome. One feature was independence of bioelectric activities of the two hemispheres, and the other was periodicity. We detected independence of bioelectric activities of the two hemispheres and the presence of abnormal discharges in both hemispheres, but did not see periodicity in five consecutive EEGs of our case.

Prognosis is poor in Aicardi syndrome. Although one case survived until at least 15 years of age, all other cases died within the first decade –most within the first several years– because of respiratory infections[2,5]. Psychomotor retardation is evident and seizures are intractable, as in our patient.

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