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Case Report

West syndrome and mosaic trisomy 13: a case report

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Trisomy 13, or Patau syndrome, is a rare chromosomal disorder characterized by a triad of cleft lip and palate, postaxial polydactyly, and microphthalmia, with an incidence ranging between 1/5,000 and 1/20,000 births.[1] Most patients (80%) with Patau syndrome have complete trisomy 13. Mosaic trisomy 13 is very rare; it occurs in only 5% of all patients with the trisomy 13 phenotype.[2] Trisomy 13 is a clinically severe entity, and 90 to 95% of patients born with this syndrome do not survive beyond one year of life. However, patients with mosaic trisomy 13 usually have longer survival and less severe phenotype compared to patients with complete trisomy 13. Malformations mainly affect midline development, with a high frequency of central nervous system involvement. The presence of central nervous system malformations is important as a predictive factor of survival.[1,3] It is well known that the incidence of epilepsy is higher in children with Patau syndrome than in the general population, and West syndrome or infantile spasms have been rarely reported in these children.[1,4,5] Prior to our report, there has been no case report of West syndrome associated with mosaic trisomy 13. The association of West syndrome with trisomy 13 is considered a symptomatic West syndrome because of preexisting psychomotor development delay and the poor prognosis in most of these children.[6] We report here the first case of West syndrome in a girl with mosaic trisomy 13 and discuss the clinical characteristics and prognosis of this association.**[Paediatr Indones. 2018;58:146-50; doi: http://dx.doi.org/10.14238/pi58.3.2018.146-50]**.

Keywords: *West syndrome; Patau syndrome; mosaic trisomy 13; prognosis*

The Case

A 4-month-old girl followed from birth for mosaic trisomy 13 developed repetitive flexor spasms, and was hospitalized in the Department of Paediatrics. She was the seventh child of healthy, non-consanguineous parents with 3 girls and 3 boys in good health. Her mother was 39 year old, the course of pregnancy was normal, and antenatal ultrasounds showed no anomalies. She was delivered vaginally at 42 weeks of gestation without incident. Apgar scores at 1 and 5 min were 8 and 9, respectively. She had dysmorphic features suggesting Patau syndrome with microcephaly, hypertelorism, upslanting palpebral fissures, epicanthal folds, broad nasal bridge, bilateral cleft lip and palate, and short neck (**Figure 1**). Transfontanellar ultrasound, abdominal ultrasound, and echocardiogram were normal. The cytogenetic examination of lymphocytes demonstrated a mosaicism of 47, XX, + 13 [6] /46, XX [10].

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Her psychomotor development at 3 months was abnormal with hypotonia and poor head control. Thyroid function was normal. At 4 months, she had flexor spasms several times a day, occurring in series, psychomotor developmental delay, and axial hypotonia. The EEG showed hypsarrhythmia. She was diagnosed as having West syndrome, and treated with Vigabatrin at a dose of 150 mg/kg/day. Vigabatrin therapy was immediately effective with good clinical control of spasms, but the EEG monitoring after one month was unchanged showing persistent hypsarrhythmia. Brain magnetic resonance imaging (MRI) showed lobar holoprosencephaly and callosal agenesis (**Figure 2**).

Because of her severe psychomotor delay, she received nasogastric tube feedings at home and the cleft lip and palate were untreatable. The first intervention of the cleft lip and palate was made at 16 months of age, but the post-operative course was marked by dropping of sutures. After a follow-up of 2 years, the patient had hypotonia, feeding difficulties, severe growth retardation, microcephaly, severe developmental delay, and tetraparesia. Her spasms disappeared with Vigabatrin. She died of pneumonia at the age of 26 months.

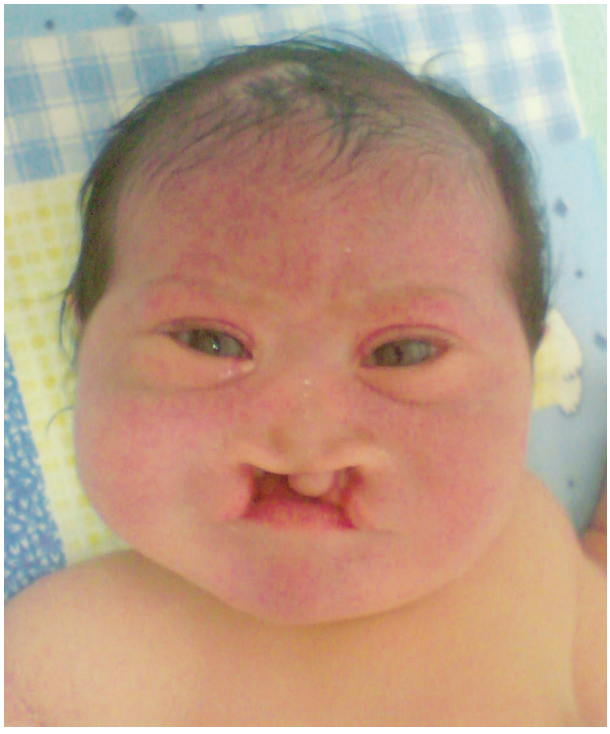

Figure 1. Facial view of the patient at birth showing hypertelorism with a large nasal bridge and a bilateral cleft lip and palate.

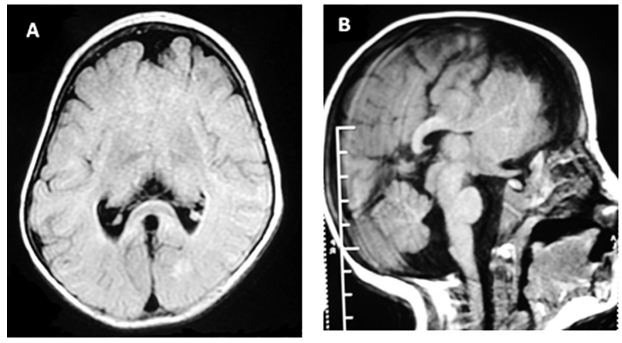

Figure 2. Brain MRI showing (A) holoprosencephaly and (B) callosal agenesis

Discussion

Mosaic trisomy 13, or mosaic Patau syndrome occurs when there is a portion of trisomic cells for an entire chromosome 13, while the remaining body cells are euploid.[7] The typical phenotype of complete trisomy 13 is usually associated with characteristic physical anomalies such as microcephaly, scalp defects, holoprosencephaly, microphthalmia, orofacial clefting, congenital heart defects, polydactyly, and profound mental retardation.[3] However, the phenotype of mosaic trisomy 13 varies widely, which renders clinical diagnosis difficult. Some patients may have the typical phenotype of trisomy 13 with neonatal death, while others may have few dysmorphic features and prolonged survival. The reason for this variation is that the phenotype changes according to the distribution of abnormal cells in specific tissues.[7] We clinically diagnosed our patient as having complete trisomy 13 by typical features, but chromosomal analysis revealed mosaic trisomy 13.

In the general population of children, the incidence of West syndrome ranges from 0.6 to 4.5 per 10,000 live births.[6,8] However, this incidence is much higher in children with Patau syndrome. It has been reported that 25 to 70% of patients with Patau syndrome have epilepsy, and 62.5% of these patients have epileptic spasms. They may present at an early age with myoclonic jerks and/or infantile spasms.[1,3,7] Spagnoli *et al.* reported that the age at onset of infantile spasms in 8 patients with trisomy 13 ranged from 2

months to 3 years and 9 months. West syndrome began during the first year of life in 50% of these patients.[1] Our patient had infantile spasms at 4 months.

The higher risk of West syndrome in Patau syndrome is shared with numerous other chromosomal abnormalities as in Down syndrome,[9] but the mechanism is not yet clear. According to the literature, two different hypotheses have been established.[1] The first hypothesis is based on the presence of malformations of cortical development in these conditions of mosaic trisomy 13. Malformations mainly affect midline development, with a high frequency of central nervous system involvement, including corpus callosum anomalies, ventriculomegaly, neural tube defects, hydrocephalus, holoprosencephaly, cerebellar dysplasia, olfactory aplasia, and cortical dysplasia. Interestingly, co-existing reflex and spontaneous seizures have been described in the setting of cortical malformations.[3,10,11] Brain MRI is recommended to facilitate the etiologic diagnosis of infantile spasms in patients with Patau syndrome.[4,6] In our patient, the brain MRI showed lobar holoprosencephaly and callosal agenesis. The second hypothesis involves genes on chromosome 13 for epilepsy and photosensitivity, and is supported by past research studies.1,12 Of interest is the recent indication of glypican-5 (GPC5) as a candidate gene for epilepsy inside the 13q31.[3] locus. Speculation has been made about a contribution of disrupted axon guidance and synaptic formation in the genesis of epilepsy and/or brain malformations in trisomy 13. However, at present, this hypothesis remains unproven.[1,12]

The diagnosis of West syndrome is often easy when infantile spasms are associated with arrest or regression of psychomotor development, and a specific EEG pattern of hypsarrhythmia.[8] The clinical symptoms of infantile spasms are very different from any other type of seizure because of the absence of paroxysmal motor phenomena, such as convulsions or loss of consciousness. This lack of typical seizure phenomena may lead to initial misdiagnosis of infantile spasms by pediatricians at the first medical consultation. Auvin **et al.** reported that approximately one-third of infants with infantile spasms were not suspected of having epilepsy during the first medical consultation.[13] Infantile spasms in infants are usually symmetrical and manifest as repetitive flexor, extensor, or flexor–extensor spasms, with sudden and brief axial contraction, predominantly in the upper limbs, with upper deviation of the eyes. In their cohort of 8 patients with Patau syndrome, Spagnoli et al. found a high prevalence of spasms and photic-induced myoclonic jerks and confirmed that photosensitivity manifested at an unusually early age of onset.[1] In our patient, West syndrome was clinically diagnosed from the flexor spasms that occurred several times a day, which began at an early age.

Medical treatment of infantile spasms should be effective and initiated as early as possible. Evaluation of treatment effectiveness includes cessation of spasms, resolution of hypsarrhythmia on the EEG, and reduction of the cognitive decline associated with epilepsy. Currently, vigabatrin and adrenocorticotropic hormone (ACTH) are the only drugs approved to suppress clinical spasms and abolish hypsarrhythmia. Past studies have reported different treatment protocols, but the large majority of children with infantile spasms received vigabatrin as first line treatment and ACTH as second line treatment.[6,14] Epileptic spasms in children with Patau syndrome were described as well-controlled with anticonvulsants.5 However, Spagnoli *et al.* presented evidence of difficult seizure control in two patients: one patient who needed multi-drug therapy and another patient who at clinical follow-up at 2 years of age experienced around 20 episodes of myoclonic seizures/day, despite high doses of sodium valproate. Neither of these patients underwent brain imaging.[1] In our patient, vigabatrin was immediately effective, with a complete resolution of clinical spasms during the first two years. The response to treatment has been shown to be significantly better when initiated less than 6 weeks after the diagnosis of infantile spasms.[15] These results suggest that early diagnosis and rapid treatment can improve longer-term prognosis of infantile spasms in children with Patau syndrome.

Despite early diagnosis and rapid initiation of effective treatment, West syndrome in children is still associated with a poor, long-term prognosis. Long-term follow-up showed that 60% of the children had drug-resistant epilepsy and that 75% had delayed psychomotor development.[16] Children with West syndrome and evidence of pre-existing developmental delay or neurological abnormalities, as in our patient, have a worse prognosis, poorer response to treatment, and less favorable developmental outcome.[6]

It is important to acknowledge that the prognosis of Patau syndrome is very poor and most patients die soon after birth because of severe congenital heart disease and brain anomalies. Almost 50% of cases die in the first month, and 90 to 95% of patients do not survive beyond one year of life. In the absence of severe cardiac and cerebral malformations, in particular the absence of holoprosencephaly, 5 to 10% of patients with trisomy 13 live longer than one year.[17,18] However, patients with mosaic trisomy 13 usually have longer survival and less severe phenotype compared to patients with complete trisomy 13. There have been several cases of long survival in patients with Patau syndrome, ranging from 3 to 38 years old.[1,3,10,18,19] Most of these survivors suffered from severe psychomotor delay, feeding difficulties, profound learning disability, seizures, as well as motor and mental deficits.[1,10,18] The patients who received intensive treatments survived longer and had better prognoses.[20,21] Although our patient had mosaic trisomy 13 syndrome, the control examination at 2 years of age showed severe developmental delay and tetraparesia.

The spectrum of phenotypic variations in mosaic trisomy 13 cases is broad. Therefore, genetic counseling of expecting parents with prenatally diagnosed mosaic trisomy 13 remains difficult. The majority of physical anomalies tend to be mild and non-life-threatening. Developmental delays and/or mental retardation, while being quite common, are not present universally. In all children with Patau syndrome, early developmental intervention and continued follow-up is essential for maximizing their cognitive skills.[10,22]

Patau syndrome patients are at increased risk of seizures. They may present at an early age with infantile spasms, but the spasms might not be easily controlled with antiepileptic medication.[1] This report describes the clinical characteristics and prognosis of a patient with mosaic trisomy 13 who survived for a relatively prolonged period and developed infantile spasms at an early age that were well-controlled with anticonvulsants.

Conflict of interest

None declared.

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