Long-Term Survival and Late Onset Seizures in an Adolescent with Trisomy 13

Francois Dominique Jacob, Vijay Ramaswamy, Hanna Kolski

Patau syndrome is a severe genetic disorder that was defined in 1960 by Patau as a trisomy of chromosome 13[1]. The spectrum of anomalies includes severe central nervous system (CNS), limb, ocular, cardiac, uro-genital involvement and facial dysmorphisms[2]. The incidence of this rare entity has been estimated at approximately 1:5000 births or 1:20000 live births. Although it is considered the third most viable trisomy after Down's syndrome (Trisomy 21) and Edward's syndrome (Trisomy 18), the vast majority of affected infants die early in life. The median survival is between 2.5 days[3] and 8.5 days, and 82-91% of affected children have been observed to die within the first year of life[4]. Common central nervous system anomalies include a high incidence of holoprosencephaly, with varying degree of development of the forebrain and olfactory and optic nerves. Seizures, severe mental retardation and apneic spells in early infancy are also common. Long survival in affected individuals has been reported in the past. Individuals typically function at a 6-12 month-old level. They are severely to profoundly mentally handicapped and have very low motor skills[5,6]. In this article we report a case of long survival in a 19-year-old girl with Patau syndrome presenting with new onset seizures at the age of 15 years.

CASE REPORT

A 15-year-old girl presented to the emergency room with a history of stiffening and jerking spells for the past month. Her mother observed the child to stiffen the left upper extremity with a low amplitude clonic movement. She had cessation in breathing and perioral cyanosis. The events would last 30 seconds to two minutes in duration, with a post-ictal period of one hour. They started with an observed frequency of one event per week evolving to one to two events per day. All the events were stereotypical. She had been otherwise well, with no intercurrent illness. She had been diagnosed at birth with Trisomy 13, based on her clinical features (right micro-ophthalmia, microcephaly with sloping forehead, broad nose, and low set ears) and confirmed via genetic testing. She was the first child of non-consanguineous Caucasian parents, with a negative family history of genetic disorder or seizure disorder. She was born at 38 weeks gestation via C-section. Her main medical concern had been recurrent urinary tract infections and hydronephrosis for which she was taking Nitrofurantoin on a prophylactic basis. She has microcephaly, right micro-ophthalmia, right-sided blindness, and bilateral cataracts; the left cataract had been removed surgically. She has global developmental delay and scoliosis. She is non-verbal and is ambulatory with the help of a walker. She had never previously
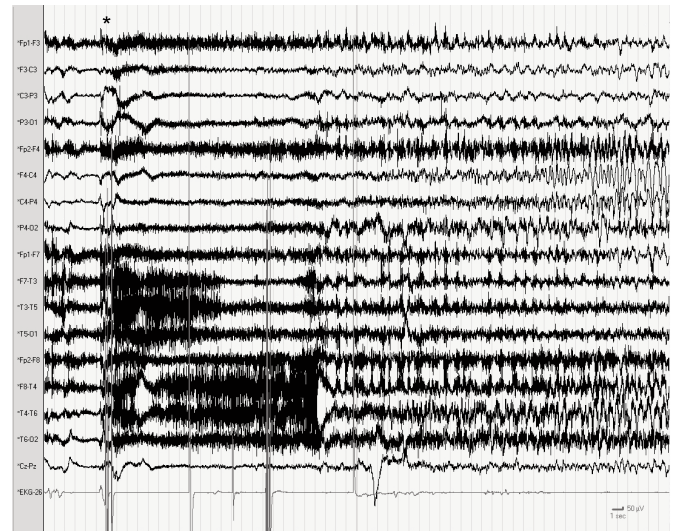

Figure 1: *Longitudinal Bipolar montage. Presumed seizure onset indicated by *. Representative baseline background encompassed prior to this point (generalized slowing). There is substantial muscle and movement artifact for approximately 20 seconds before convincing rhythmic activity becomes apparent in the right hemisphere (most obvious frontally). Sensitivity 15 uv/mm. Low filter 0.5 Hz. High filter 35 Hz. Paper speed 60 seconds/page.*

had any seizure type activity or periods of paroxysmal unresponsiveness. She was dependent on all activities of daily living. She was orally fed. Her only other medications were Depo-Provera for menstrual control and a laxative to help with chronic constipation. Physical examination revealed a head circumference of 51 cm (<< 2nd percentile). Visual fields could not be reliably assessed. Cranial nerve examination was otherwise normal. There were no facial dysmorphic features suggestive of holoprosencephaly (hypotelorism, cleft lip/palate, a flattened nasal bridge and/or a single central incisor). Motor
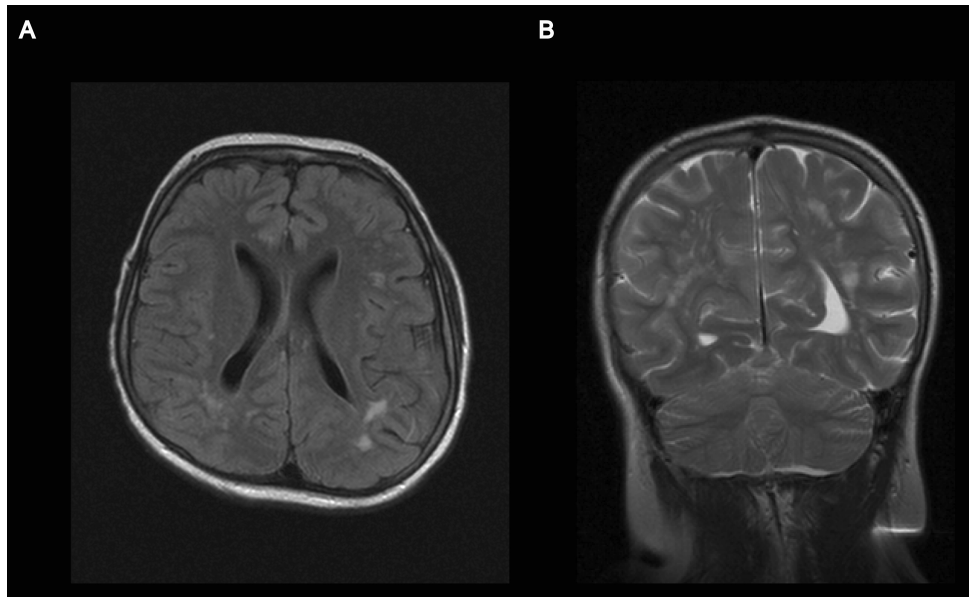
Figure 2: MRI A) Axial FLAIR image at the level of the centrum semiovale, B) Coronal T2 weighted image at the level of the occipital horn of the lateral ventricles, revealing multiple hyperintense lesions in the subcortical white matter of both cerebral hemispheres.

exam revealed mild contractures at the shoulders, elbows, wrists, and knees. She had pes cavus feet bilaterally. There was mild spasticity in the upper and lower extremities. The deep tendon reflexes were normal and symmetric. Both plantars were downgoing. She could sit independently and generally moved around by crawling. She could stand on her own and take steps with a walker.

Investigations included an electroencephalogram (EEG) and cerebral imaging. A representative clinical event was captured on EEG (Figure 1) consisting of: rhythmic movement of the left arm, followed by a gasp and tonic posturing of the left arm, perioral cyanosis and subsequent tonic extension of all limbs. The event lasted approximately 90 seconds. The precise seizure onset was obscured by muscle and movement artifact. Ictally a build up of rhythmic activity was seen over the right frontocentral region. Interictal background is generally very poorly differentiated, and slow more so in the right hemisphere. Magnetic Resonance Imaging (MRI) of the head (Figure 2) revealed multiple patchy areas of increased T2/FLAIR signal measuring between 3 and 7 mm in the subcortical white matter bilaterally. More confluent areas of abnormal signal were present in the posterior temporal and parietal lobes. The basal ganglia appeared normal and no focal cortical abnormalities were identified. Investigation revealed normal complete blood count, electrolytes and vitamin B12 levels. A thyroid stimulating hormone (TSH) level was slightly elevated at 4.62 μIU/mL. Cerebrospinal fluid (CSF) examination including lactate was normal. Karyotyping was repeated and performed according to routine protocol. Thirty metaphases with 650-band resolution were analyzed and confirmed the neonatal diagnosis of trisomy 13. Further genetic testing was declined by the family.

She was started on Clobazam, a long acting benzodiazepine. Her seizures were initially fully controlled, however Lamotrigine was added one year later because of an increase in seizure frequency. She is now 19 years-of-age, clinically stable and has remained seizure free.

DISCUSSION

Survival above ten years of age is rare in cases of Trisomy 13. There have been eight reported cases since Patau first defined the entity[7-13]. These cases all represent full Trisomy 13 with no evidence of mosaicism. Cases of long survival in individuals with mosaic Trisomy 13 have also been reported[14,15]. However there is no clear association between the level of mosaicism, the severity of the phenotype and potential survival at birth[15]. A repeat karyotype in the presented case confirmed her neonatal diagnosis, which would exclude levels of mosaicism of 10% or greater with 95% confidence[16]. Although further genetic testing was declined by the family, Delatycki and Gardner[15] have reported that individuals with mosaicism infrequently have features classically associated with non-mosaic Trisomy 13. Our case showed dysmorphic features consistent with Trisomy 13 as described in the case report. She represents the third longest survival, the longest being a 32-year-old women reported by Tunca et al.[11]

Seizures and epilepsy are common occurrences in affected individuals with Trisomy 13. They have been described as minor motor seizures, often with a hypsarrhythmic pattern on the EEG[2]. In his review of the natural history of this condition, Baty[5], found that 52% of the patients had evidence of a seizure disorder. In cases of long survival, five out of the eight patients, including this case, had epilepsy. The seizure types reported varied from

generalized tonic-clonic, myoclonic jerks, atonic seizures, to absence epilepsy. All seizures began in infancy with the exception of one patient with delayed onset epilepsy at the age of four[9]. Electroencephalogram findings reported include; diffuse epileptic discharges[9], focal slowing, bilateral synchronous spike and wave complex, polyspike discharges[9], and predominant theta rhythm[12]. The etiology of epilepsy in individuals with Patau syndrome has not been defined, but has been assumed to be secondary to the genetic defect, and associated cerebral malformations.

Reports of neurological autopsy of infants with Trisomy 13 reveal the presence of CNS malformations such as holo-prosencephaly, cerebral and cerebellar dysplasia, cerebellar heterotopia and polymicrogyria, as well as meningeal glioneural heterotopia on the surface of the brain and pons[17-20]. In our presented case, the MRI study did not show clear cortical abnormalities or malformation but reveals numerous white matter lesions of unknown significance. There are no reports of characteristic neuroimaging features in individuals with Patau syndrome and long survival. Previous computed tomogram scan studies in two cases have revealed: moderate dilatation of the ventricular system and bilateral basal ganglia calcifications[9], a mild dilatation of the ventricular system, mild cortical atrophy and atrophy of the cerebellar vermis[12]. There was no evidence of holoprosencephaly. Confounders in these cases include congenital heart disease in the former and severe intrapartum asphyxia in the latter. Clinically two individuals had a cleft lip and/or palate with no other features suggestive of holoprosencephaly, one of which had a normal pneumo-encephalogram[8]. It is generally felt that the lack of holoprosencephaly or significant CNS malformation has contributed to these individuals long survival. The observed white matter hyperintensities in our patient are non-specific. Considerations included demyelinating or dysmyelinating processes, vasculitides and various metabolic abnormalities. Further CSF studies failed to corroborate these possible etiologies. This represents the first MRI imaging in an affected individual later in life. The areas of T2 hyperintensity may possibly represent aberrant white matter development, however in the absence of serial imaging from birth, it is difficult to know if these lesions are congenital or acquired.

In summary, this case represents the 3rd longest surviving patient with Trisomy 13 and the oldest to develop epilepsy. This case expands the clinical and radiological spectrum of the Trisomy 13 phenotype beyond the first decade of life. It remains unclear why her seizure onset is so late. We hope this report can prompt further assessment of the natural history, neuroimaging and pathology in Trisomy 13, and alert clinicians that seizures can be a late finding in children who survive past the first decade of life.

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