

## Clinical report

### Patient 1:

A 7-year-old girl, the first child of non-consanguineous healthy Caucasian parents, was born at 40 weeks of gestation after a normal pregnancy. Birth weight 4010 gram (90<sup>th</sup> centile), birth length 54 cm (95<sup>th</sup> centile) and head circumference 38 cm (95<sup>th</sup> centile). APGAR scores were 8 at both 1 and 5 min of life.

Within a few hours after birth, she was admitted to the neonatal intensive care unit due to poor sucking, severe hypotonia and epileptic seizures. She presented with tonic and myoclonic seizures with apnea, both of which repeatedly turned to convulsive status epilepticus (CSE). Seizures were refractory to multiple antiepileptic drugs including phenobarbital (PB), levetiracetam (LEV), valproic acid (VPA) and midazolam (MDZ). After two months, she was discharged from the neonatal ward but she was still experiencing recurrent seizures despite treatment with a combination of PB, LEV, VPA and oxcarbazepine (OXC). In the following years she had intractable myoclonic and tonic seizures with secondarily generalization despite combinations of PB, vigabatrin, LEV, VPA, topiramate (TPM), OXC, MDZ and diazepam. Currently she is treated with TPM, OXC and clobazam and has approximately twenty monthly events with either brief tonic seizures and deviating eye movements or tonic-clonic seizures with apnea that last around one minute. Her initial electroencephalogram (EEG) performed at two weeks of age showed multiple bilateral bursts of spike-and-waves. She was frequently admitted to the hospital because of CSE induced by fever, recurrent episodes of respiratory infections or urinary tract infections. The interictal EEG at the age of four years of age showed diffuse background slowing and focal slowing as well as frequent spike and slow waves predominant in the fronto-temporal regions, bilaterally asynchronously. On video EEG polygraphic recordings have been documented frequent episodes of central apnea (up to 10 sec), mainly during NREM sleep but sometimes also during wakefulness, without EEG correlate.

By the age of nine months, significant developmental delay was evident: she had poor head control, was not fixing or following, had head lag when pulled to sit and made no attempt to elevate her head when prone. At the age of 7 years she is profoundly delayed. She is unable to sit or stand on her own but she is able to make eye contact and smile. She has no meaningful words and her sleep cycle is disorganized. Since the age of twenty months she has been dependent on a permanent feeding tube. Ophthalmological examination revealed cortical visual impairment and abnormal motility of the eyes including strabismus and nystagmus. Auditory examination showed normal hearing.

Minor dysmorphic features were noted shortly after birth including a depressed nasal bridge, an anteverted nose and a long philtrum. However her dysmorphic features became more evident over time and at latest evaluation (Figure 2A) they included brachycephaly with bitemporal narrowing, telecanthus, a long and distinct philtrum, a small tented mouth with a high and arched palate, full cheeks, a depressed nasal bridge and a short anteverted nose. Scalp hair and eyebrows were sparse, the eyebrows were straight (Figure 2A and figure S1). She also presented with hypertrichosis (Figure S1). Tooth eruption was delayed and the teeth were small and widely spaced (Figure 2I). She also exhibited joint hypermobility, overlapping toes and skeletal abnormalities. A systematic skeletal survey performed at 76 months of age illustrated skeletal abnormalities including an S-shaped scoliosis, slender osteopenic long bones, bilateral

dislocated hips with a shallow acetabulum and dysplastic distal phalanxes in both feet (pictures not shown). The bone age was normal.

An echocardiography and an ultrasound of the kidneys performed at thirteen months of age were normal. Brain MRI was performed at three days (Figure 4A-B), three months (Figure 4C-D), nine month (Figure 4E-F) and four years of age (Figure 4G-H) showed delayed myelination, atrophy of the white matter supratentorially and a severely hypoplastic corpus callosum. There were no signs of cerebellar atrophy.

Metabolic screening included plasma amino acids, lactic acid, pyruvic acid, organic acids, lysosomal enzymes and these were all unremarkable. Analysis of the urine for mucopolysaccharides and oligosaccharides also showed normal results. Standard karyotyping and a SNP 6.0 array were both normal. She had normal levels of alkaline phosphatase, plasma calcium, plasma phosphate and parathyroid hormone. Due to the hypertrichosis blood levels of 17-hydroxyprogesterone, cortisol and adrenal steroids were measured and were found to be normal.

#### **Patient 2:**

Patient 2 was the younger brother of patient 1. He was born at 39 weeks of gestation following an uneventful pregnancy. Birth weight 3685 gram (50<sup>th</sup> centile), birth length 54 cm (90<sup>th</sup> centile) and head circumference 36 cm (50<sup>th</sup> centile). APGAR scores were 8 at both 1 and 5 min of life.

Following birth, he was admitted to the neonatal intensive care unit due to severe hypotonia and within a few hours he developed epileptic seizures. He showed tonic and myoclonic seizures with apnea and frequent episodes of CSE. His seizures were also refractory to multiple antiepileptic drugs including PB, LEV, VPA and midazolam while the seizures decreased with the combination of PB, LEV, VPA, TPM and OXC. After 1½ months he was discharged from the neonatal ward. In the following months he experienced treatment resistant brief or longer lasting myoclonic and tonic seizures with secondary generalization. Prior to his death, he was treated with LEV, carbamazepine and PB. A ketogenic diet was never tried. EEG performed at two weeks of age showed multiple bilateral bursts of spike-and-waves. The EEG at follow up showed diffuse background slowing/destructuration and continuous delta activity and spike-and-slow waves bilaterally with clear predominance in the posterior quadrants. He had (non-epileptic) central apneas during NREM sleep.

Following the neonatal period there were no significant psychomotor gains. He had a poor head control, was not fixing or following, had head lag when pulled to sit and made no attempt to elevate his head when prone. Ophthalmological examination revealed cortical visual impairment and abnormal motility of the eyes including strabismus and nystagmus. Auditory examination showed normal hearing. He had dysmorphic features including brachycephaly with bitemporal narrowing, telecanthus, a long and distinct philtrum, a small tented mouth with a high and arched palate, full cheeks, a depressed nasal bridge and a short anteverted nose (Figure 2B). Scalp hair, eyebrows, and eyelashes were sparse, the eyebrows were straight (Figure 2B), and the nails were short and friable (Figure S2). Tooth eruption was delayed and the teeth were small and widely spaced (pictures not available). Furthermore, he exhibited pectus excavatum (Figure S2) and joint hypermobility. At eleven months of age he died of pneumonia.

Brain MRI performed at thirteen days of age (Figure 4I-J) showed delayed myelination and a hypoplastic corpus callosum. Ultrasound of the kidneys and an echocardiography was never performed.

Metabolic screening included plasma amino acids, lactic acid, pyruvic acid, organic acids, lysosomal enzymes and these were all unremarkable. He had normal levels of alkaline phosphatase, plasma calcium, plasma phosphate and parathyroid hormone. A systematic skeletal survey was never performed, however X-ray of the chest revealed a slender long right humerus bone (Figure 4I).

**Patient 3:**

First female child of healthy consanguineous Asian parents born at 39+5 weeks gestation by forceps assisted delivery. Intrauterine growth retardation was noted during the pregnancy and her birth weight was 2380g (0.4<sup>th</sup> percentile). Head circumference at birth was not recorded but at two weeks of age it was 33cm (9<sup>th</sup> percentile) and her weight was 2690g (below 0.4<sup>th</sup> percentile). Apgar scores were 3 at 1 min and 10 at 5 min and she required stimulation and oxygen but no ventilatory support. At birth she was noted to be centrally and peripherally hypotonic, weak and areflexic with multiple joint contractures. She required nasogastric tube feeding. She was transferred to the department of pediatrics at 2 weeks of age for further evaluation of a suspected neuromuscular disorder. Brief myoclonic jerks were noted and an EEG showed a burst suppression pattern with brief myoclonic jerks as well as subtle focal seizures of right and left temporal onset. She did not respond to trials of biotin, pyridoxal phosphate, TPM and LEV. She remained severely hypotonic, encephalopathic and did establish neither a social smile nor meaningful visual behavior. At six months of age she died following central sleep apnea and cardiac arrest at home.

Her MRI scan showed absence of myelination in the posterior limbs of the internal capsule and signal change in the basal ganglia bilaterally indicating a possible neuro-metabolic disorder (pictures not shown). Her electromyography and nerve conduction patterns were normal. An echocardiography and an ultrasound of the kidneys were normal. A skeletal survey was never performed. An ophthalmological examination was done at three weeks of age and was not followed up again.

An extensive neurometabolic screen including bloods for creatinine kinase, lactate, ammonia, aminoacids, transferrin isoforms, very long chain fatty acids, urate, acylcarnitines, vacuolated lymphocytes, electron microscopy of the buffy coat, urine for purine screen, and organic acids, CSF lactate, neurotransmitters, pyridoxal phosphate and aminoacids were all negative. She had normal levels of alkaline phosphatase. Clinical pictures of this patient were not available and the description of her dysmorphic features was based on the patient files.

**Patient 4:**

This patient was a 2-year-old girl, the first child of non-consanguineous parents of Polish origin. The family history was unremarkable for birth defects, intellectual disability or other genetic diseases. The girl was born spontaneously at 39

weeks of gestation with a length of 56 cm (97<sup>th</sup> centile), weight of 4150 g (90-97<sup>th</sup> centile) and head circumference at 36 cm (50<sup>th</sup> centile). Weight, length and head circumference progressed in the normal range and her current measures are

length 91 cm (75<sup>th</sup> centile), weight 12.7 kg (50<sup>th</sup> centile) and head circumference OFC 50 cm (75-90<sup>th</sup> centile).

At 18 months of age she experienced her first tonic-clonic seizure. She was initially treated with VPA and responded well but did not become seizure free. Therefore LEV was added to the treatment which has so far kept her free from seizures. Her initial EEG performed at the age of 18 months was normal. At the age of 4 years the EEG showed focal slowing and spike/polyspikes-and slow waves in the left fronto-centro-temporal region.

During the first year of life a muscular hypotonia and a marked psychomotor developmental delay was noticed. At 28 months her development was profoundly delayed. She had just learned to sit but was unable to stand on her own and had no meaningful words. An ophthalmologic evaluation had revealed a severe bilateral hyperopia. Her MRI scan showed a mild cerebellar hypoplasia and in addition a suprasellar cystic tumor. The tumor was surgically removed and subsequent histological investigation showed that it was an adamantinomatous craniopharyngioma (WHO grade 1).

An extensive neurometabolic screen including bloods for creatinine kinase, lactate, ammonia, aminoacids, transferrin isoforms, very long chain fatty acids, urate, acylcarnitines, urine for purine screen, and organic acids were all negative. She had normal levels of alkaline phosphatase.

Her dysmorphic features included a high forehead with sparse hair, a high frontal hairline, and bitemporal narrowing. A small nose with a depressed nasal bridge, tented upper lip, cupid bow lips were prominent (Figure 2C).

#### **Patient 5:**

The proband, a currently 7-years-old girl, was born after an uneventful second pregnancy at 38 weeks of gestation by cesarean section because of mother's orthopedic indications. Body weight was 4810 g (>95<sup>th</sup> centile), length was 57 cm (>95<sup>th</sup> centile), and occipito-frontal head circumference was 38 cm (>95<sup>th</sup> centile). The family history was unremarkable for birth defects, intellectual disability or other genetic diseases. There is healthy daughter from the first pregnancy. The parents were young, healthy and non-consanguineous. Both Apgar's scores were normal and the neonatal period was uneventful. Horizontal nystagmus and astigmatism (+8.5D) with visual impairment were diagnosed at 8 months of age. Clinical evaluation at 10 months showed psychomotor retardation with muscular hypotonia and a severe delay in motor development. At the age of 11 months she started to experience febrile generalized febrile tonic-clonic seizures coincident with upper respiratory infection. The seizures typically lasted 2-5 minutes. Due to a high frequency of epileptic seizures a treatment with VPA was initiated at the age of 18 months. Currently she is still on VPA and has been seizure free since the treatment was initiated although at the age of 6 years following a head injury she experienced a short generalized tonic-clonic. Her EEG in awake performed at 3 and 7 years of age showed background slowing 4-7 Hz (the basal function of the parietal-occipital region consists of amplitude up to 70uV with low-voltage fast action) without epileptiform abnormalities.

At the age of 7 years, an MRI showed a mild hypoplasia of the lower part of cerebellar vermis, mild hypoplasia of cerebral hemispheres with a cystic dilatation of the fourth ventricle and an enlarged posterior fossa corresponding to a Dandy - Walker malformation.

Ultrasonography of the abdomen as well as an echocardiographic evaluation was normal. EEG investigation indicated abnormal excess of slow waves in the temporo-occipital region with multifocal epileptiform abnormalities. An extensive neurometabolic screen including bloods for creatinine kinase, lactate, ammonia, aminoacids, transferrin isoforms, very long chain fatty acids, urate, acylcarnitines, vacuolated lymphocytes, electron microscopy of the buffy coat, urine for purine screen, and organic acids, CSF lactate, neurotransmitters, pyridoxal phosphate and aminoacids were all negative. She had normal levels of alkaline phosphatase. Slight hyperglyceridemia was noted. Chromosome analysis showed a normal karyotype of 46, XX at 500-band, and no CNVs were found in microarray-based comparative genomic hybridization (array CGH – CytoSure Constitutional v3 resolution 120kb, Oxford Gene Technology). Neurologic examination showed mild hypotonia with joint hypermobility with tremor of the hands. Deep tendon reflexes were normal and pathologic reflexes were absent.

At 7 years of age she was still unable to walk. She had a mild degree of intellectual disability and difficulties with speech and articulation. Her dysmorphic features included a brachycephalic headshape with a high forehead. Scalp hair and eyebrows were sparse with a high frontal hairline. She had upslanting palpebral features, telecanthus, arched eyebrows, slightly depressed nasal bridge, prominent and long philtrum, cupid bow lips with prominent lower lip and a high palate (Figure 2D).

#### **Patient 6:**

She is the five years younger sister of patient 5. She was born after an uneventful third pregnancy at 37 weeks of gestation by cesarean section because of mother's orthopedic indications. Body weight was 3380 g (>75<sup>th</sup> centile), length was 53 cm (>95<sup>th</sup> centile), and occipito-frontal head circumference was 36 cm (>95<sup>th</sup> centile). Apgar scores were normal. Shortly after birth nystagmus with strabismus and poor visual contact was found. At the age of 7 months, the first myoclonic-tonic generalized seizures with breathing disturbances and ocular movements occurred. Treatment with VPA was immediately implemented. At the age of 18 months, her EEG showed discrete background slowing and sporadic high amplitude spike-and-slow wave complexes in the left fronto-temporal region or bilaterally in the frontal regions.

During the neonatal period, an abdominal ultrasound, an echocardiography and a brain MRI did not reveal any abnormalities. Results of biochemical, hormonal and metabolic investigations, among others plasma amino acids, lactic acid, pyruvic acid, organic acids, lysosomal enzymes were all unremarkable. She had normal levels of alkaline phosphatase, plasma calcium, plasma phosphate and parathyroid hormone.

Neurologic examination at 19 months of age showed muscle hypotonia and an inability to sit without support. She is still seizure free but is kept on antiepileptic treatment. Her dysmorphic features included a brachycephalic headshape with a high forehead. Scalp hair and eyebrows were sparse with a high frontal hairline. She had upslanting palpebral features, telecanthus, arched eyebrows, slightly depressed nasal bridge, prominent and long philtrum, cupid bow lips with prominent lower lip and a high palate (Figure 2E).

#### **Patient 7:**

The proband is an 11 years old male born to a consanguineous Somali parents. He was born following a normal pregnancy by emergency Caesarean section at 42 weeks of gestation because of fetal distress. His birth weight was 4.32 kg (95<sup>th</sup> centile) and his occipito-frontal head circumference was 35.5 cm (69<sup>th</sup> centile). There were no perinatal problems. He had vomiting and gastro-oesophageal reflux from 2 months of age. He developed generalized seizures initially associated with fever from 6 months of age however from one year of age the seizures were atypical and associated with a prolonged recovery phase. By 22 months he had developed atonic seizures. An EEG at that time showed suspicious paroxysmal discharges and associated sharp waves. A repeat EEG showed multiple bilateral bursts of spike-and-waves discharges. An MRI brain scan was normal. His seizures were refractory to LEV, VPA and LMT and they continued on combined treatment with zonisamide, clobazam (CBZ) and TPM. His seizures have almost completely ceased on commencing a ketogenic diet and he has discontinued his anti-convulsant medication. He has had recurrent chest infections. He had a patent ductus arteriosus and an aneurysmal fossa ovalis however a follow up echocardiogram at the age of 2 years was normal. The results of metabolic and biochemical investigations including calcium and alkaline phosphatase levels were normal. He has a normal recent renal ultrasound scan.

He was referred for assessment at 6½ months of age because of developmental delay and hypotonia. At 18 months he had head lag when pulled to sit. He could however sit with support, push up on his arms when prone and roll. He could reach out with a palmar grasp and transfer object and put them into his mouth. He had no hand dominance. He had five words and understood simple instructions. He could finger feed and eat lumpy foods. At 22 months he could sit independently and weight bear. He has been able to crawl from 4 or 5 years of age. Currently he can stand holding onto furniture for short periods of time. He communicates using simple signs and by pointing and he understands simple instructions. He makes high pitched sounds and he has repetitive mannerisms and will clap his hands together if excited. His hearing and ophthalmological assessments have been normal. He attends special school.

He had a weight of 40 kg (73<sup>rd</sup> centile) and a head circumference of 51.5 cm (2<sup>nd</sup> centile). He had marked truncal hypotonia and increased peripheral tone and reflexes. He had ridging of the sagittal suture. He had a wide forehead and bitemporal narrowing. He had slightly wiry hair, straight eyebrows, mildly downslanting palpebral fissures and infraorbital creases. He had a broad nasal bridge and short anteverted nose. He had a tented mouth with down turned corners and a high arched palate. His ears were round, low set and posteriorly rotated. He had slightly puffy hands and feet. His chest, abdomen and spine were normal.

#### **Patient 8:**

Patient 8 was the younger brother of patient 7. He was born at 29 weeks gestation. He had developmental delay hypotonia and myoclonic seizures. He had visual impairment, a left hemiplegia, and increased hypotonia following pneumococcal meningitis and septicaemia. He appeared facially similar to patient 7. He had the familial homozygous PIGT mutation. He also had an older sister with a similar presentation including developmental delay, hypotonia and seizures and who died at 15 months of age from a chest infection. His parents had a son born at 30 weeks gestation

that died at 3 weeks of age with multiple problems related to prematurity and four first trimester miscarriages. They have one healthy developmentally normal daughter. Further clinical data was not available.

**Patient 9:**

This girl, now 6 years and 9 months, is the elder sister of patient 10. Her parents are from Somalia and recently became aware that they are consanguineous. She was born by elective Cesarean section for breech presentation with a birth weight of 3450 g (>99<sup>th</sup> centile), and head circumference 37.4 cm (>99<sup>th</sup> centile).

When reviewed in the Genetics Clinic at 1 year 9 months she is able to sit for a few minutes and weight bear with some help from her parents.

On examination we noted head circumference was on the 90<sup>th</sup> centile with a length between 71<sup>st</sup> to 91<sup>st</sup> and weight on the 91<sup>st</sup> centile. She was able to interact visually, though convergent squint was noted. She was still centrally hypotonic. The prominence of the forehead was less than previously noted. Facially, we noted the relatively flat nasal bridge, mild epicanthus and tented upper lip.

Her first seizure was around 10 months affecting the left side and then progressed to more frequent seizure with myoclonic jerks.

Video fluoroscopy had shown aspiration, therefore she was on thickened feeds. She had tonsils and adenoids removed to help her mild obstructive sleep apnoea.

She did not have any history of early tooth loss, she had cardiology review which showed small patent ductus but no abnormality of cardiac muscle, check renal ultrasound treatment for epilepsy sodium valproate and Levetiracetam.

**Patient 10**

This male baby was born at 41 weeks by elective Caesarean section with birth weight of 3580 g (>99<sup>th</sup> centile) and head circumference of 37 cm (>96<sup>th</sup> centile). There was a history of polyhydramnios in pregnancy. He developed persistent vomiting at 8 hours of age with abdominal distention and he was observed by the surgical team but did not require any intervention.

Neurological features at that time were poor fixing and following, tremulous, jerky movement and hyperreflexia at both the upper and lower limbs. He had an EEG which did not reveal any epileptic activity and an MRI reporting widely patent cavum septum pellucidum, some dilatation of the fourth ventricle and rotation of the cerebellar vermis away from the brainstem though the vermis was anatomically normal.

On review at three months of age, he was unable to hold his head steady. He had increased tone in both upper and lower limbs bilaterally. Bilateral brisk reflexes more pronounced in the lower limbs. Examination of the spine was normal and he was not thought to have any dysmorphic features.

When he was reviewed in genetics at seven months of age, he was getting less stiff and trying to reach for objects but not yet sitting or rolling. As his neurological and physical features (relative macrocephaly with scaphocephaly and tented upper lip) were in keeping with his older sister an exome analysis was arranged.

His growth and clinical features are outlined in the table. He developed seizures from just under a year of age which became more difficult to control. He had a combination of myoclonic jerks and generalised tonic-clonic seizures.

He did become increasingly unwell with recurrent chest problems and bronchiolitis and difficult to control epilepsy, and died at the age of two years and two months during one of these emergency admissions to hospital.

**Patient 11:**

This patient is the second child of unrelated parents. She was born by vaginal delivery at 42 weeks after a pregnancy complicated by vaginal bleeding at around 7 and 12 weeks. She weighed 3990 g (91<sup>th</sup> centile) and there were no immediate concerns at birth. She had some tremulous movements as a young baby and was noted to have unusual eye movements from the first week of life, with upward deviation of her eyes and poor fixing and following.

She had three seizures in the context of a febrile illness when she was around a year old. Initially this was attributed to encephalitis but CSF studies were normal. At this time her EEG was noted to be slow, and a convalescent EEG also showed bilateral slow activity but no clear epileptiform abnormalities. She was later diagnosed with epilepsy after she went on to experience further seizures, with her predominant seizure type being generalised tonic clonic seizures (often associated with febrile illnesses). Over time she achieved good seizure control with VPA.

She developed a left renal stone when she was around a year old. X-rays of her wrist and knee showed no evidence of metabolic bone disease, and a 24-hour urine collection for citrate, calcium, oxalate and urate showed normal excretion of all of these. Her plasma calcium phosphate and urate were normal as was her calcium and magnesium. The renal stone was initially conservatively managed but this became impacted aged 3 years, at which point she had left ureteroscopy and fragmentation of the stone.

She was diagnosed with global developmental delay as she was late to start rolling and unable to sit until she was 15 months old. She went on to develop marked ataxia and serial MRI scans demonstrated progressive isolated cerebellar atrophy affecting the vermis and hemispheres. When reviewed by neurology aged 5 years she had an alternating convergent squint, oculomotor apraxia of vertical gaze, and marked gait ataxia with bilateral limb ataxia. She has significant dysarthria and delayed expressive language. Aged 9 years, she could speak around twenty clear words. However she was very good at communicating her needs using sign language and communication aids.

On examination in the genetics clinic aged 9 years, her head circumference was 53 cm (25<sup>th</sup>-50<sup>th</sup> centile), her height was 135.5 cm (75<sup>th</sup> centile) and her weight was 32.4 kg (75<sup>th</sup> centile). She had slightly deep set eyes, a broad nasal tip, a 'cupid's bow' shape to her top lip and a pointed chin. Her hands were structurally normal. Her spine was straight. There was no unusual shape to her chest. Her palate, skin and teeth were normal.

Extensive neurometabolic investigations including full blood count, liver function tests, thyroid function, vitamin E, creatinine kinase, very long chain fatty acids, phytanic acid, urate, urine amino acids, caeruloplasmin, transferrin

glycoforms, white cell enzymes were normal. ERGs and VEPs were normal. Array CGH and Angelman testing was normal.

**Patient 12:**

First female child of healthy consanguineous Pakistani consanguineous parents born at 36 weeks gestation by forceps assisted delivery. Her birth weight was 3000g (75<sup>th</sup> percentile). Height and head circumference at birth was not recorded. Apgar scores were normal.

She presented with focal seizures at 6 months of age, associated with fever and necessitating admission to the intensive care unit. These initially responded to buccal midazolam. She progressed to having generalized tonic clonic seizures. CT on admission showed general reduction of brain volume with open opercula and thin commissures. Prior to the onset of seizures there was a history of global developmental delay and bilateral hydronephrosis with multi resistant recurrent urinary tract infections. She has a variable lymphopenia with no underlying immunological defect identified. MRI prior to onset of seizures showed delayed myelination and EEG was abnormal with generalised slowing throughout with posterior epileptiform discharges. Subsequent seizures have usually been associated with underlying infection or fever, may start as erratic myoclonus with no consistent focality. There was an improvement in seizures after introduction of VPA in addition to LVT and CBZ. Seizure frequency now approximately 25 episodes a day, up to 17 seconds and self resolving.

Ophthalmological examination revealed cortical visual impairment and abnormal motility of the eyes including strabismus and nystagmus. Auditory examination showed normal hearing. She had dysmorphic features including brachycephaly and a high forehead, telecanthus, a distinct philtrum, a tented mouth with a high and arched palate, cubid bow shaped lip and a short anteverted nose. Scalp hair were sparse. An echocardiography was normal. The results of metabolic and biochemical investigations including calcium and alkaline phosphatase levels were normal. At almost 2 years of age she remains globally delayed, hypotonic and unable to fix and follow. She has an unsafe swallow and is dependent of a permanent feeding tube.

**Patient 13:**

A 6 month-old girl now deceased, who was the first child of consanguineous healthy Bangladeshi parents. She was born at 40 weeks gestation, after a pregnancy complicated by intrauterine growth restriction. Birth weight 2380g (<0.4<sup>th</sup> centile) and head circumference 32 cm (<0.4<sup>th</sup> centile). She required inflation and ventilation breaths at birth and APGAR scores were 3 at 1 minute and 10 at 5 minutes of life.

At birth she was noted to have bilateral elbow contractures and contracture of the distal finger joints. She was admitted to the neonatal intensive care unit due to poor sucking, areflexic severe hypotonia and a presumed neuromuscular disorder. She was noted to have facial twitching and myoclinic jerks, which prompted an EEG demonstrating a burst suppression pattern. Seizures were refractory to multiple antiepileptic drugs with trialing of pyridoxal phosphate, LEV and TPM. She was discharged from the neonatal ward with ongoing seizures. By the age of 3 months she had developed intermittent dystonic movements of the lower limbs and had suffered recurrent chest infections. She died at the age of 6 months.

She was thought to be non-dysmorphic on examination at 3 weeks of age. An echocardiography and an ultrasound of the kidneys performed at three weeks of age were normal. Brain MRI was performed at 2 weeks of age and showed abnormal T1 signals in the globi pallidi bilaterally and absent myelination in the posterior limbs of the internal capsule. Metabolic screening included plasma amino acids, lactic acid, pyruvic acid, organic acids, lysosomal enzymes and were all unremarkable. Analysis of the urine for mucopolysaccharides and oligosaccharides also showed normal results. CSF neurotransmitters and biotinidase were normal. She had normal levels of alkaline phosphatase, plasma calcium and plasma phosphate.

**Patient 14:**

Patient 13 was the older sister of patient 12. She was born at 39 weeks gestation by normal vaginal delivery. Her birth weight was 2400g (0.4<sup>th</sup> percentile) and birth length was 32cm (<0.4<sup>th</sup> percentile). The head circumference at birth was not recorded. Apgar scores were normal. Within a few hours after birth, she was admitted to the neonatal intensive care unit due to poor sucking, severe hypotonia and epileptic seizures. She presented with generalized tonic seizures with apnea and was treated with LEV. Do to pain and swelling of the extremities a series of x-ray were carried out and showed that she had three major fractures of her humerus, femur and wrist. A supplementary skeletal survey found signs of healing fractures of the right humeral and right femoral diaphyses. Subtle periosteal reaction along the midshaft of the left humerus and subtle contour abnormality at the anterior ends of the left seventh and eighth ribs were also found and could represent fractures. Bone density appeared diffusely reduced. During her hospital stay, her condition remained the same and she was finally discharged home with palliative care plan. She continued to have seizures although they are short lived and mainly involve eye flickering and facial grimacing. She is currently 4 months old and has made only little developmental progress since. She has not sustained further fractures.

The EEG showed diffusely attenuated background activity with burst-suppression pattern and interburst intervals lasting up to 8 seconds. Bursts contained multifocal sharp elements and clinically correlated with eye blinking, oral movement and twitching of the extremities.

Her MRI scan performed during the first month of life was normal. An echocardiography and an ultrasound of the kidneys were normal. Due to feeding difficulties she is dependent on a permanent feeding tube. Ophthalmological examination was normal but an auditory examination has not been carried out.

She had normal levels of alkaline phosphatase. Clinical pictures of this patient were not available and the description of her dysmorphic features was based on the patient files.