## *Clinical reports*

**Patient 1** (Dr Edery) is a 19 year-old-girl, daughter of healthy and unrelated parents. She was born in France by cesarean section due to breech presentation after an uneventful pregnancy ending at 40 weeks. Growth (2,880 kg, -1 SD), lenght (47 cm, -2 SD), head circumference (OFC) (33 cm, -1 SD) and adaptation to extra-uterine life were normal at birth. Oral intolerance and jaundice were noticed, leading to tube feeding in neonatal period. Developmental milestones and growth were normal until 6 months when axial hypotonia and global growth deceleration were noted. Head growth declined leading to severe acquired microcephaly (-4 SD) noticed at 7 months. Weight and length deceleration resulted in a global hypotrophy (-3 SD). Cerebral tomodensitometry at age of 7 months showed a mild global cortical and subcortical atrophy. Brain MRI was no performed in this young girl. There was no hand use and manual stereotypies (hand-to-mouth or hand-to-eyes) were present since the first year of life. At last re-evaluation at 19 years of age, patient 1 could lift her head but she was unable to sit or walk and no language was acquired. She presented with bruxism, inexplicable episodes of laughing and mild convergent bilateral strabism. Facial features were not specific, with synophris, lingual protrusion and sialorrhea. Eye contact and visual behaviour stayed normal. Breathing and sleeping patterns were normal and she did not showed any peripheral vasomotor disturbances. Patient 1 presented with moderate orthopaedic deformations consisting of scoliosis and flat feet. Notably, she had no history of seizures.

**Patient 2** (Dr Rivier) is a five-year-old male who was born in France by spontaneous delivery after an uneventful pregnancy. He presented with normal neonatal parameters with a relative small OFC (33 cm, -1 SD). In the neonatal period, he developed a severe congenital encephalopathy with severe hypotonia, severe feeding difficulties and hypersomnia. He

presented with inconsolable crying, opisthotonos and poor eye contact. Postnatal deceleration of head growth resulted in severe microcephaly (-2 SD at 2 months of age, and -5 SD at 5 years). Infantile spasms began when he was 1 year old. Vigabatrin was efficient, the spasm vanished with an improvement of attentiveness. Refractory myoclonic epilepsy appeared a few months later leading to epileptic encephalopathy. Background activity was slow, without any spatialisation. Bilateral intercritic photoinduced sharps where frequent. At 2 years of age, EEG pattern changed in an intermittent hypsarrythmia in light and deep sleep, with delta sharp waves. Corticosteroids improved myoclonic seizures, which disappeared at 4 years. At 18 months brain magnetic resonance imaging (MRI) revealed agenesis of the corpus callosum, enlarged lateral ventricles and poor myelin formation in sub-cortical frontal brain region. Hand stereotypies (hand-to-mouth and symmetric movements at the midline) appeared at the age of 3 years. At last examination at the age of 5 years he could not sit alone and presented with a movement disorder consisting of dyskinesia, dystonia and chorea. Mild dysmorphic features were noted with synorphis, bilateral epicanthus, large ears, short and large nose, short philtrum, slight micrognathy, down-turned corners of the mouth, high palate and thin fingers.

**Patient 3** is a 15-year-old French girl (Dr Amsallem), first child of non consanguineous healthy parents. Microcephaly was detected by routine ultrasonography during the fourth month of pregnancy. She was born at 38 weeks gestation by spontaneous delivery after an uneventful pregnancy with normal neonatal parameters: birth weight 2790 g (-1SD), length 47 cm (-1 SD), and OFC 32 cm (-2 SD). From birth, she presented with sucking and swallowing difficulties, inconsolable crying mostly present at night and poor eye contact. A persistent poor eye contact led to an ophthalmic examination at the age of 4 months. The vision was normal and no strabismus was noticed. Until the age of 5 months babbling were normal but she never smiled, even to her parents. At 5 months, axial hypotonia and peripheral hypertonia

signed a pyramidal syndrome with poor spontaneous motricity. Head growth deceleration led to a severe -4 SD microcephaly. There was no real regression of neurological state. At 1 year of age the patient couldn't sit unaided, a better eye contact was noticed. She acquired purposeful hand skills that were lost soon after. Epilepsy started at 7 months with up to hundred myoclonic seizures per day, controlled by sodium valproate. Interictal awaken recordings were normal. At 1 year of age, infantile spasms and atypical absences seizures appeared and responded well to medication (vigabatrin added to sodium valproate). Epilepsy seemed to be controlled by lamotrigine up to age 5. Interictal awaken recordings were too slow with paroxysmal bioccipital and vertex sharp waves of high voltage, without clinical signs, similar to those often described in RTT patients. At 5 years she developed partial seizures, with both frontal and medial temporal components. There were always myoclonic episodes. Lamotrigine was stopped at 10 years, the patient was treated with sodium valproate and topiramate without recurrence of seizure. Cerebral MRI at 3 years of age revealed bilateral frontal atrophy. Corpus callosum was normal. At the age of 15 years, axial hypotonia remained and she could not sit. Neither walking nor language was acquired. The patient presented inconsolable crying and unexplained laughing episodes, she focused attention more on objects than toward social partners. Manual stereotypies bothered hand skills. During adolescence, she developed gastrointestinal disturbances consisting of severe constipation due to anorectal dyskinesia, feeding difficulties, and gastroesophageal reflux disease with teeth lesions. Important undernutrition led to home tube feeding and gastrostomy with nissen fundoplication. Patient 3 presented with global bone decalcification on X-rays. Thoracolumbar scoliosis was corrected by surgery when the patient was 14 years old. She did not exhibit cold extremities, there is no history of breathing or sleeping disturbances.

**Patient 4** is a 26-year-old female who was born in France (Dr Lambert) at 39 weeks gestation by spontaneous delivery after an uneventful pregnancy. Neonatal parameters were normal:

weight 3.3 kg (50$^{th}$ percentile), length 48 cm (-1 SD), OFC 34.5 cm (50$^{th}$ percentile), Apgar scores 8/ 9. At birth, she presented with axial hypotonia and hypertrichosis on neck and back, she was very quiet. No other members of her family were affected by hypertrichosis. She lifted her head at 2 months. She was referred at the age of 4 months because of hypotonia and head growth deceleration, leading to -2 SD microcephaly. Brain MRI at 3 years revealed agenesis of the corpus callosum with frontal atrophy. Walking and language were never acquired without any neurological regression. Generalized seizures appeared at 14 months, easily controlled by sodium valproate. Severe constipation started at the age of 4 years. She had a surgical treatment for scoliosis when she was 14 years old. At last examination at the age of 26 years, she can't lift her head anymore and is severely mentally retarded. Head growth deceleration led to a severe acquired microcephaly (-4 SD). There is a good non-verbal contact with hand stereotypies worsened by anxiety. Her tongue is protruding and she grinds her teeth. Notably, her body temperature is always low (<35°C) with asymmetrically cold and blue extremities. She falls asleep when her body temperature is below 33 °C. She has thin skin and tapering fingers. . EEG data were not available for this patient.

**Patient 5** is a 6-year-old girl who was born in Belgium (Dr Destree) from healthy and consanguineous parents after an uneventful pregnancy. At birth, she was small for gestational age: weight 2240g (-3 SD), length 44 cm (-3.5 SD) and OFC 29 cm (-4.5 SD). She underwent cardiac surgery for interventricular communication. She had feeding difficulties, she was not able to walk until the age of 30 months. At re-evaluation at 5 years of age, she could only speak a few words. She was severely microcephalic (-5.5 SD) with a body weight of 13kg (-3 SD) and length of 102 cm (-2 SD), EEG was normal. She had minor dysmorphic facial features consisting of upslanted palpebral fissures, bilateral epicanthal folds, retromicrognathia, and dysplastic ears. She was described like a shy child, without any

autistic features. Brain MRI demonstrated a poor myelination with hypoplasia of the corpus callosum and deformation of the third ventricule.

**Patient 6** is an 8-year-old Australian boy (Drs Harbord and Thompson) born after a normal pregnancy and a delivery by elective Caesarian section at term (Apgar scores 9 and 9). He is the second child of healthy Caucasian parents. He had normal neonatal parameters (weight and length on 50$^{th}$ percentile) but relatively small OFC (-1 SD). She presented with a congenital stridor due to laryngomalacia. At 4 months of age, he presented with microcephaly and delayed development. During the first year, the picture evolved to global developmental delay and spactic quadriparesis. He developed severe epilepsy with a seizure onset at 8 months. At last evaluation at nearly 8 years, he stood with support, could not walk unaided, had no speech and had severe microcephaly (-4 SD). He had marked choreoathetoid and dystonic movements of limbs, uncontrolled tongue protruding movements but no bruxism and was having about 3 seizures per week despite anticonvulsant therapy (Topiramate). The general examination was unremarkable, he was not dysmorphic and had normal genitalia. Brain MRI at 4 years of age demonstrated a small brain with hypoplasia of the corpus callosum, hypoplasia of the cerebelar vermis and reduction of the white matter tract mainly in the front lobes. EEG data were not available for this patient.

**Patient 7** is a ten-year-old French boy (Dr Bieth) born by spontaneous delivery after an uneventful pregnancy with normal neonatal parameters. He is the only child of non consanguineous parents. Development was considered as normal until the age of 6 months when he presented with axial hypotonia. On first examination at 11-month-old, he presented with severe developmental delay, axial hypotonia, choreoathetosis, acquired microcephaly (-4 SD) and mild postnatal growth deficiency (-2 SD for weight and length). Abnormal genitalia combined micropenis and cryptorchidy. The diagnosis of Angelman syndrome was considered in a boy who was jovial with inappropriate laughing. Molecular evaluation of

15q11-q12 methylation pattern was normal. Brain MRI at 11 months showed normal brain morphology. At the age of 2 and ½ years, he developed self-agressivity. Age of onset of epilepsy was 28 months with generalized tonic-clonic seizures. At the age of 3 years he became seizure-free on a combination of micropakine and rivotril. Later on, he developed febrile seizures that evolved in atonic or dystonic refractory seizures. *ARX* and *MECP2* screening were negative. A second brain MRI at 6 years of age revealed poor myelin formation in frontal-subcortical brain. At the age of ten, he presents with pyramidal symptoms, he is not able to walk and did not develop any language. According to the parents he makes constant progress and improves social reciprocity. . EEG data were not available for this patient.