

Supplemental Data

Supplemental Note: Case Reports

Individual 1

Individual 1 is a 10 year old female with epilepsy, autism and language delay. She was born at 37 weeks gestational age via C-section due to maternal diabetes. Growth parameters at the time of last evaluation at 9 years of age included OFC of 55.5cm (>97%ile), weight of 80.7kg (100%ile) and height of 145.4cm (86%ile). She has been diagnosed with obesity. Hearing and vision assessments were normal. Her first words were at 3 years of age, and presently she does not speak in full sentences. She has also been diagnosed with autism. She receives PT, OT, ST and also has an IEP at school which includes special education. She has frontal lobe epilepsy, with EEG demonstrating L frontal focal epileptiform abnormalities. Brain MRI demonstrated a 3mm area of T2 signal abnormality in the inferior left temporal lobe. Cardiac evaluation was normal.

Individual 2

Individual 2 is a 28 year old male who presented with focal onset status epilepticus at age 8. He was diagnosed with ADHD and mild cognitive impairment prior to the onset of epilepsy. He had short stature but otherwise normal growth parameters. By age 9, he developed drug resistant epilepsy with seizures arising from the left temporal lobe. MRI showed bilateral posterior temporooccipital lobe cerebral calcifications and white matter T2/FLAIR hyperintense foci involving the left temporal lobe. Left temporal lobe resection at age 9 for intractable epilepsy demonstrated ILAE Type IIb focal cortical dysplasia characterized by presence of dysmorphic and balloon neurons (Figure 2). After surgery, there were no further generalized tonic clonic seizures, but other seizures continued. His course has subsequently been characterized by progressive neurocognitive dysfunction, epilepsy, stroke-like episodes particularly of the occipital lobes, cortical visual impairment, suspected transient ischemic attacks with vision loss or weakness/R facial droop. His seizures are characterized by (1) visual hallucinations lasting up to hours with retained impairment, (2) staring and unresponsiveness, and (3) rare generalized tonic clonic activity. He has transient episodes of unclear etiology with sudden full loss of vision in both eyes or inability to walk lasting several minutes with nearly complete resolution. Brain MRIs have shown progressive occipital white matter hyperintensities and subcortical white matter T2/FLAIR hyperintense foci that progressively evolved over time to cystic encephalomalacia with volume loss of the occipital lobes (Figure 2). In addition to multiple antiepileptic medications, he was treated with IVIG and mycophenolate mofetil which decreased the frequency of the episodes for a presumed autoimmune condition despite negative autoantibodies. He also has kidney stones with end stage kidney failure, bradycardia of unclear etiology with normal echocardiogram. He is employed part-time at a grocery store.

Individual 3

Individual 3 is a 5-year-old male with epilepsy and global developmental delay. He was born at 37 weeks via induced vaginal delivery. Growth parameters at delivery included weight of 3232g (74%ile, Z-score 0.63) and length of 45.7cm (14%ile, Z-score -1.06). At time of last evaluation at 3 years of age, OFC was at 20%ile (Z-score 0.86), weight was at 29%ile (Z-score 0.55) and height was at 15%ile (Z-score 1.00). No facial dysmorphisms were noted. Hearing and vision evaluations were normal. However, developmental abnormalities were reported in all domains requiring physical therapy and speech therapy. Although he walked at 15 months he was noted to lack balance. He demonstrated left hand preference at 12 months of age. He said his first word at 15 months of age and was not speaking in full sentences at 3 years old, however speech rapidly improved with placement of myringotomy tubes. He also required G-tube feedings until 3 years of age. He developed temporal lobe epilepsy, with EEG demonstrating seizures arising from the left temporal lobe. Brain MRI, however, was normal. Bloodwork demonstrated elevated transaminases, therefore liver biopsy was performed, demonstrating abnormal mitochondria on electron microscopy, absence of complex I activity, decreased complex IV activity, and abnormal complex V assembly. Cardiac evaluation was normal.

Individual 4

Individual 4 is a 7 year old girl with global developmental delay, behavioral problems as well as movement disorder. She was born at 41 weeks gestational age by vaginal delivery. She was noted to be macrocephalic at birth, and weighed 3940g (74%ile). At the time of last evaluation, OFC was 54cm (>97%ile), weight was 29.8kg (92%ile), and height was 124cm (67%ile). On exam she was noted to have bitemporal narrowing, high palate and hypotonia. She demonstrated poor latch and choking in infancy, which progressed to oral dysphagia by age two, thereby necessitating placement of a G-tube by which she receives all nutrition. The most recent swallow evaluation within the last year was normal. She was also diagnosed with severe central and obstructive sleep apnea at 14 months of age. She underwent tonsillectomy and adenoidectomy but was not able to tolerate BiPAP. Presently her central sleep apnea has mostly resolved. Although she walked on time around 13-14 months of age, she is noted to be clumsy and displays toe walking. She does not use any tools such as utensils. She spoke her first words around 12 months of age but subsequently stopped gaining new words, and now is non-verbal aside from the use of an augmentative communication device for single word communication. She was initially diagnosed with sensorineural hearing loss, however at age 4 was found to have normal hearing at which point hearing aids were discontinued. She has been diagnosed with severe autism and has self-injurious behaviors, intense tantrums, rigidity, aggression, poor emotional regulation, and poor frustration tolerance. She also displays stereotypic movements diagnosed as possible tic disorder. She receives PT, OT, ST and ABA, and also receives special education. The most recent brain MRI at 5 years old demonstrated stable small pars intermedia pituitary cyst, as well as mild diffuse thickening of the corpus callosum. EEG at 5 years old was normal. ECHO and EKG were normal. Holter monitor demonstrated sinus bradycardia.

Individual 5

Individual 5 is an 18-year-old male with mild intellectual disability and language impairments. He was born at 40 weeks by vaginal delivery. Growth parameters at birth included weight of 3317g (29%ile, Z-score -0.54). He had poor latch in infancy, and as an older child has frequent GI symptoms concerning for irritable bowel syndrome. He was noted to have fine motor difficulties as well as difficulties with verbal communication. Hearing and vision evaluations were normal. He has also been diagnosed with ADHD and mild intellectual disability, although he did not receive therapy services or special education. At time of last evaluation at 18 years of age, OFC was 53cm (<3%ile), weight was 57kg (13%ile), and height was 185cm (89%ile). Malar hypoplasia, prominent jaw, arachnodactyly, pectus carinatum, pes planus, mild kyphosis, and cryptorchidism were noted on exam. Brain MRI was normal. ECHO demonstrated mild dilation of the ascending aorta. Marfan/LDS panel was sent, demonstrating paternally-inherited VUS in COL5A1. Bloodwork demonstrated decreased level of IgA.

Individual 6

Individual 6 is a 2 month old full-term boy with epilepsy and sleep apnea. He was born at 40 weeks gestational age by spontaneous vaginal delivery. Growth parameters at delivery were OFC of 36cm (75%ile), weight of 3480g (43%ile) and length of 47cm (3%ile). At time of most recent evaluation at 2 months of age, OFC was 40.5cm (65%ile), weight was 4920g (31%ile) and length was 57.5cm (40%ile). Exam demonstrates mildly low axial tone. No facial dysmorphisms were noted on exam. He passed a hearing screening on day of life 1. On day of life 3 he developed focal seizures characterized by staring, paucity of movement, apnea, profound desaturation and whole-body cyanosis. EEG captured 2 focal seizures arising from the left occipital region which evolved to spread into the left temporal region. Brain MRI on day of life 5 demonstrated trace right posterior convexity subdural hematoma, but was otherwise unremarkable. Sleep study at 15 days old demonstrated moderate to severe central apnea and mild obstructive apnea, requiring continuous supplemental oxygen by nasal cannula. Modified barium swallow study at 16 days old demonstrated aspiration, which resolved with use of preemie flow nipple.

Individual 7

Individual 7 is an 8 month old male with G-tube dependence and multiple congenital anomalies. Congenital heart disease was diagnosed prenatally. He was born via C-section at 38 weeks gestational age due to breech presentation, prolonged rupture of

membranes, and known congenital heart disease. Growth parameters at delivery included weight of 3.18kg (36 %ile), length of 50cm (52%ile) and OFC of 33cm (12 %ile). He was diagnosed with tetralogy of Fallot with severe pulmonary stenosis and small right ventricular outflow tract. He also was found to have cleft palate, Pierre-Robin sequence, right inguinal hernia and unilateral cryptorchidism. Other facial dysmorphisms include downslanting palpebral fissures, epicanthal folds, large protruding ears, long philtrum, downturned mouth and micrognathia. Full developmental assessment is limited due to his age, however he appears to have gross motor delays as at 5 months of age he was unable to roll over or push himself up when prone. He is also G-tube dependent. Due to concerns for abnormal movements an EEG was obtained, which was normal.

Individual 8

Individual 8 is a 9 year old female with epilepsy, ADHD and psychiatric abnormalities. She was born via C-section at 40 weeks gestational age. Birth weight was 3260g (38%ile) and length was 48.3cm (17%ile). At time of last evaluation at 9 years of age OFC was 51.5cm (~62.5%ile), weight was 25.8kg (25%ile) and height was 129cm (26%ile). She developed epilepsy at 15 months of age, necessitating VNS placement. Several EEGs have demonstrated both generalized and focal interictal activity. Brain MRI at around 5 years old was unremarkable. She has been diagnosed with ARFID and failure to thrive, necessitating G-tube placement. She also has ADHD, anxiety, depression, and behavioral outbursts. She receives occupational therapy for fine motor difficulties. She has an IEP at school which includes special education, and is currently performing at the kindergarten level despite being in second grade for the second time.

Individual 9

Individual 9 is a former 31 week gestational age male who died at 6 months of age. He was delivered via C-section due to non-reassuring fetal heart tones. At birth OFC was 30.7cm (94%ile), weight was 2720g (100%ile) and length was 44.5cm (94%ile). A hearing assessment was normal. On exam he was noted to have dysconjugate gaze, hypertelorism, long eyelashes, upturned ears with fleshy lobes and mid-lobe indentation, short, upturned nose, and wide philtrum with deep grooves. At 6 months of age, OFC was 45.5cm (89.93%ile), weight was 9.8kg (96.14 5%ile) and length was 61.2cm (0.51%ile). He had numerous congenital anomalies including severe pulmonary vein stenosis, enlarged left kidney with cortical cyst, duodenal atresia, esophageal atresia with tracheoesophageal fistula, biliary atresia with absent gallbladder, and imperforate anus with rectocutaneous fistula. He ultimately underwent G-tube placement. Head ultrasound demonstrated subventricular hemorrhage. He subsequently was diagnosed with portal hypertension, cholestasis, necrotizing enterocolitis, ascites, abdominal abscesses. A cholestasis gene panel demonstrated likely pathogenic variant in TTN gene. He died at 6 months of age due to pulmonary hypertension secondary to pulmonary vein stenosis.

Individual 10

Individual 10 is a 18 year old male with language delays, ADHD and autism. He was born at term after induction of labor. Growth parameters at delivery included weight of 3460g (41%ile) and length of 51cm (47%ile). Audiology evaluation at 5 years of age was normal. At the time of last evaluation at 9 years old, his weight was 27.2kg (38%ile) and height was 138.2cm (77%ile).

Individual 11

Individual 11 is a 6 year old female with epilepsy, autism and speech delay. She was born at 39 weeks gestational age by vaginal delivery. At birth, she weighed 2920g (24.1%ile). At the most recent evaluation at 5 years of age, OFC was 48.2cm (2.78%ile), weight was 17kg (35%ile) and height was 109cm (61%ile). Exam was notable for deep-set eyes, long philtrum and full cheeks. In terms of development, she was noted to have speech delay necessitating speech therapy. She was ultimately diagnosed with autism. She also displays disruptive behaviors at school. Presently she is not receiving special education. She has been diagnosed

with epilepsy, with EEGs demonstrating left occipital epileptiform discharges as well as mild diffuse background slowing. Brain MRI reportedly demonstrated right hippocampal atrophy.

Individual 12

Individual 12 is a 19-year-old female with global developmental delay, intellectual disability and ADHD. She was born at 37 weeks via vaginal delivery. Weight at delivery was 2140g (5%ile, Z-score -1.66). She was noted to have gross motor delay and severe language delay, not walking until 20 months and not speaking until 12 years old. She was ultimately diagnosed with mild intellectual disability requiring special education and speech therapy. She also has fine motor difficulties. She was diagnosed with ADHD and noted to have several psychiatric abnormalities including anxiety, self-injurious behavior and behavioral disorder. At time of last evaluation at 19 years of age, OFC was 55cm (50%ile), weight was 46.1kg (5%ile, Z-score -1.62), and height was 158.9cm (8.7%ile, Z-score -1.36). Facial dysmorphisms were noted, including long face, broad forehead, epicanthus and hypertelorism with low set ears, narrow palate, bulbous nose and thick lips. Evaluation of hearing was normal, however she was noted to have strabismus. Brain MRI was normal.

Individual 13

Individual 13 is a 10 year old male with autism, ADHD, language delay, and psychiatric abnormalities. He was born at 40 weeks gestational age. Weight at time of delivery was 3345g (32%ile) and length was 49.5cm (23%ile). Exam demonstrates cryptorchidism as well as wide nasal bridge, broad nasal tip, and a long upper lip. He demonstrated delayed language acquisition for which he required speech therapy. His first words were at 2 years of age and he did not speak in sentences until around 4 years of age. He also displayed fine motor delays. He was diagnosed with autism, ADHD, anxiety, and also has auditory hallucinations. He is currently receiving special education.

Individual 14

Individual 14 is a 5 year old girl with global developmental delay and ADHD. She was born at 38 weeks gestational age following an uncomplicated delivery. Growth parameters at birth included OFC of 32cm (13%ile), weight of 2530g (12%ile) and length of 41cm (0%ile). At the time of last evaluation at 4 years of age, OFC was 42.5cm (<3%ile), weight was 9.9kg (0%ile), and height was 84.4cm (0%ile). She is currently undergoing evaluation for growth hormone therapy. Exam at that time demonstrated mildly low hanging columella, proximally placed thumb, and 5th finger clinodactyly. She has had normal cardiac evaluation, renal ultrasound, and brain MRI. She demonstrated delays in all domains and requires PT and OT. She has been diagnosed with ADHD which is being treated with stimulant medication as well as an IEP at school.