Summary of patients with pathogenic CNVs

As showcased below, we have segregated patients with significant CNVs according to their Beaudet category of pathogenicity. We have outlined the patient number within the cohort, age, sex, type of CNV and locus, and a statement on their clinical presentation. Where appropriate, the microdeletion or microduplication syndrome is stated. Where no such established syndrome is known, a brief summary of their overarching phenotype is described.

**Table e-1. Beaudet Category 1.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Patient Number | Age | Sex | Microdeletion / Microduplication | CNV locus | Clinical Features | Description of Syndrome |
| 56 | 2 | M | Microdeletion | 5q14.3q23.1 | Mild global DD, dysmorphism, generalised epilepsy, periventricular nodular heterotopia on MRI | 5q14.3 Microdeletion Syndrome |
| 75 | 18 | M | Microdeletion | 22q13.33 | Moderate global DD/ID, ASD, focal and generalised seizures, | Phelan-McDermid Syndrome |
| 119 | 5 | M | Microdeletion | 5q14.3 | Severe global DD/ID, cortical visual impairment, dysmorphism, microcephaly, generalised myoclonic epilepsy in infancy with status epilepticus and medically refractory seizures, spasticity, periventricular leukomalacia with dysplastic corpus callosum on MRI | 5q14.3 Microdeletion Syndrome |
| 189 | 6.5 | F | Microdeletion + Microduplication | 4p16.3p14 / 10q26.2q26.3 | Severe global DD/ID, dysmorphism, microcephaly, ataxic cerebral palsy with cerebellar hypoplasia on MRI | Severe neurological disability with ataxic cerebral palsy |
| 277 | 13 | F | Microduplication | Xp22.3q28 / 19q13.32q13.43 | Severe global DD/ID, dysmorphism, microcephaly, epilepsy with recurrent non-convulsive status epilepticus and medically refractory seizures, spastic quadriplegic cerebral palsy | Severe global neurological disability with seizures and cerebral palsy |
| 310 | 23 | M | Microduplication (Triplication) | Xq11.1q13.2 | Moderate global DD/ID, dysmorphism | FG Syndrome |
| 312 | 6 | M | Microdeletion | 15q11.2q13.1 | Severe global DD/ID, microcephaly, generalised tonic seizures, dystonic movement disorder | Angelman Syndrome |
| 314 | 6.5 | M | Microdeletion | 15q11.2q13.1 | Severe global DD/ID, cortical visual impairment, dysmorphism, atonic seizures with epileptic encephalopathy, hypotonia | Angelman Syndrome |

**Table e-2. Beaudet Category 2.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Patient Number | Age | Sex | Microdeletion / Microduplication | CNV locus | Clinical Features | Description of Syndrome |
| 2 | 5 | M | Microdeletion | 9q21.1q21.2 | Severe global DD/ID, ASD, macrocephaly, absence seizures and status epilepticus, diplegic cerebral palsy and cortical malformation on MRI | Cortical lissencephaly with severe neurological disability and epilepsy |
| 8 | 14 | M | Microdeletion | 14q13.2q21.1 / 10p12.1 | Moderate global DD/ID, movement disorder, ADHD | Benign Hereditary Chorea |
| 13 | 19 | M | Microdeletion | 16p11.2 | Mild global DD/ID, benign infantile epilepsy, movement disorder | Paroxysmal Kinesigenic Dyskinesia with infantile seizures |
| 16 | 5 | M | Microdeletion | 15q13.2q13.3 | Family history of DD/ID, moderate global DD, dysmorphism | Global DD and dysmorphism |
| 24 | 12 | M | Microdeletion | 19q13.12 | Mild global DD/ID, dysmorphism, dystonia, spasticity | Generalised dystonia with spasticity |
| 25 | 14 | M | Microdeletion | 16p11.2 | Mild global DD, movement disorder | Paroxysmal Kinesigenic Dyskinesia |
| 76 | 3 | M | Microdeletion | 17p13.3 | Severe global DD, cortical visual impairment, myoclonic epilepsy with epileptic encephalopathy and medically refractory seizures, lissencephaly with frontal agyria and parietal pachygyria | Lissencephaly Miller-Dieker Syndrome |
| 109 | 1 | F | Microdeletion | 13q31.2q31.3 / 16p11.2 | Mild global DD, focal dyscognitive seizures | Focal epilepsy |
| 122 | 10 | M | Microduplication | 9q33.1 / 16p13.11 | Family history of NF1, moderate global DD/ID, neurocutaneous lesions, microcephaly, ADHD | Neurofibromatosis Type 1 |
| 124 | 5.5 | F | Microdeletion | 2q22.1 / 14q13.2q21.1 | Motor developmental delay and proximal weakness | Motor disorder |
| 195 | 2.5 | M | Microdeletion | 5q35.2q35.3 | Family history of Prader-Willi Syndrome, mild global DD, cortical visual impairment, dysmorphism, macrocephaly | Sotos Syndrome |
| 219 | 3.5 | M | Microdeletion + Microduplication | 15q21.3 / 22q11.21 | Severe global DD, dysmorphism, microcephaly, dystonic movement disorder, bilateral perisylvian polymicrogyria and periventricular nodular heterotopia | DiGeorge Syndrome (Velo-cardio-facial Syndrome) |
| 220 | 12 | F | Microdeletion + Microduplication | 8p23.3p23.1 / 8p22 / 8p22 | Mild global DD/ID, ataxia | Cerebellar Syndrome |
| 230 | 9.5 | M | Microdeletion | 2q24.3 | Moderate global DD/ID, idiopathic generalised epilepsy, ADHD | IGE within spectrum of GEFS+ or Mild Dravet Phenotype (SME-B) |
| 232 | 2 | F | Microduplication (Triplication) | 15q11.2q13.3 | Moderate global DD, ataxia | Global neurological disability with ataxia |
| 269 | 5 | F | Microdeletion | 16p13.11 | Mild global DD, infantile spasms with epileptic encephalopathy | 16p13.11 Microdeletion Syndrome |
| 278 | 19 | F | Microdeletion | 16p11.2 | Severe language delay | Severe language delay |
| 317 | 4.5 | F | Microduplication | 15q11.2q13.1 | Severe global DD, cortical visual impairment, dysmorphism, generalised tonic seizures | Tetrasomy 15q11.2-q13.1, IDIC 15 syndrome |
| 323 | 21 | F | Microdeletion | Xq22.2q22.3 | Moderate global DD/ID, ataxia, anxiety, neuropathy | Pelizaeus-Merzbacher like Syndrome with disordered CNS myelination and peripheral neuropathy |
| 437 | 19.5 | F | Microdeletion | 16p13.11 | Positive family history, severe global DD/ID, cortical visual impairment, microcephaly, generalised epilepsy with status epilepticus, epileptic encephalopathy and medically refractory seizures | 16p13.11 Syndrome |
| 440 | 18.5 | M | Microdeletion | 15q13.2q13.3 | Positive family history, moderate global DD/ID, photosensitive epilepsy with eyelid myoclonus and absence falling within spectrum of Jeavons Syndrome | 15q13.3 Microdeletion Syndrome |
| 453 | 7.5 | F | Microdeletion | 2q37.2q37.3 | Mild global DD/ID, dysmorphism | 2q37 Monosomy Syndrome |
| 460 | 7.5 | F | Microduplication | 7q11.23 | Mild language delay, macrocephaly | 7q11.2 Duplication Syndrome |
| 498 | 17.5 | M | Microdeletion | 22q12.1q12.2 | Moderate global DD/ID, sensorineural hearing loss, neurocutaneous lesions, bilateral vestibular schwannomas | Neurofibromatosis Type 2 |
| 505 | 19.5 | F | Microdeletion | 16p11.2 | Language delay | Language delay |
| 540 | 22 | M | Microdeletion | 17p13.1 | Severe global DD/ID, sensorineural hearing loss, dysmorphism, myoclonic seizures, spastic quadriplegic CP | 17p13.1 Microdeletion Syndrome |
| 553 | 5.5 | F | Microdeletion | 16p11.2 | Family history of epilepsy, mild language delay, generalised tonic clonic seizures | Epilepsy and language delay |

**Table e-3. Beaudet Category 3.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Patient Number | Age | Sex | Microdeletion / Microduplication | CNV locus | Clinical Features | Description of Syndrome |
| 3 | 18 | F | Microdeletion | 7q21.3 | Mild global DD/ID, positive family history, myoclonus dystonia movement disorder | Myoclonus Dystonia |
| 4 | 20 | F | Microdeletion | 7q21.3 | Mild global DD/ID, positive family history, myoclonus dystonia movement disorder, ADHD | Myoclonus Dystonia |
| 164 | 2 | M | Microdeletion | 16p11.2 | Strong family history of paroxysmal kinesigenic dyskinesia, infantile generalised seizures | Infantile generalised seizures, likely to manifest paroxysmal kinesigenic dyskinesia movement disorder |
| 184 | 5.5 | F | Microdeletion | 3q26.33 | Severe global DD/ID, dyskinetic cerebral palsy | Dyskinetic cerebral palsy |
| 186 | 3.5 | F | Microduplication | 18q22.1 | Mild global DD, cerebellar atrophy | Cerebellar ataxia and oculomotor apraxia |
| 222 | 4 | F | Microduplication | 6q25.1q25.2 | Severe global DD, cortical visual impairment, focal dyscognitive seizures and infantile spasms, diplegic cerebral palsy, dysplasia of brain on MRI | Disorder of neuronal migration with pachygyria |
| 226 | 6 | F | Mosaic (33% cells) Microdeletion | 22q13.2q13.33 | Severe global DD/ID, hypotonia | Phelan-McDermid Syndrome |
| 244 | 15 | F | Microduplication | 17p12 | Family history of CMT1A, anxiety, neuropathy with distal weakness | Charcot-Marie-Tooth 1A |
| 245 | 11.5 | F | Microduplication | 17p12 | Family history of CMT1A, neuropathy with distal weakness | Charcot-Marie-Tooth 1A |
| 250 | 2.5 | F | Microdeletion | 5q15q21.1 | Moderate global DD, cortical visual impairment, microcephaly, infantile spasms with epileptic encephalopathy | Neurological disability with cortical visual impairment, microcephaly and epilepsy |
| 285 | 20.5 | F | Microduplication | 16p11.2 | Family history of DD/ID, moderate global DD/ID, microcephaly, ADHD | Global DD/ID with microcephaly and ADHD |
| 361 | 3.5 | F | Microdeletion | 9q33.3q34.11 | Tonic focal seizures | Neonatal tonic focal seizures |

Definitions and tabulation of data:

For the purposes of this study, the following definitions were the criteria required to register the condition as present, and appropriate for inclusion in statistical analysis. Definitions are provided for categories beyond simple demographic data points such as name, age and date of birth.

*Parental consanguinity:* defined as the presence of a first degree relation between the mother and father of the proband. I.e. A relationship of brother and sister. This excluded cases where mother and father were first cousins or other more distant relation, as this was often difficult to accurately ascertain in the diverse ethnic background represented in the cohort.

* 1 = present, 0 = absent

*First degree family history of neurological disease:* defined as the presence of significant neurological disease in a first degree relative. I.e. Neurological disease in mother, father, brother or sister. The criteria for significant neurological disease was subjective, but included any of the 95 categories of interest within this study, as well as any medically important neurological phenotype similar to the proband.

* 1 = present, 0 = absent
* A description of the positive family history was captured in a subsequent data point, under the category heading of “details of family history”

*Developmental delay:* defined within the framework of the DSM-V criteria. In the present study, it was a diagnosis reserved for children with onset of features before the age of 5, whereby the child demonstrated significant disability in one or more domains in comparison to the expected milestones achieved by other children. These domains included gross motor, fine motor, language, cognition and social interaction. It was reserved for children under the age of 5 as this represented the developmental period during which the child could not reliably and accurately undergo formal evaluation of IQ using standardized testing. However, many of the patients in the cohort underwent a developmental assessment using tools such as the “Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III)”, “Griffiths Mental Development Scales, Extended Revised (GMDS-ER)” and the “Ages and Stages Questionnaire (ASQ)”. These assessments were carried out by a team consisting of specialist developmental paediatricians, clinical nurse specialists, social workers and clinical psychologists. Information gleaned from these developmental resources was also used in the assessment of developmental delay severity, and the type (see below).

* 1 = present, 0 = absent

*Global developmental delay:* defined as the presence of developmental delay in two or more domains outlined above. Global developmental delay was also considered to be present if indicated in the child’s Bayley-III/GMDS-ER/ASQ report.

* 1 = present, 0 = absent

*Motor delay only:* defined as the presence of persistent difficulties with gross or fine motor movements before the age of 5. This encompassed issues with posture, ambulation, and the manipulation of objects with manual dexterity, consequently resulting in a significant impact upon function. This developmental delay occurred in isolation, without any concomitant impairment in language, cognition or social interaction. Therefore, the presence of motor delay “only” was mutually exclusive with the presence of global developmental delay.

* 1 = present, 0 = absent

*Language delay only:* defined as the presence of persistent difficulties in the acquisition of vocabulary and use of fluent speech before the age of 5. These issues pertaining to the comprehension of words and pronunciation of dialogue could not be attributed to intellectual disability or global developmental delay. This developmental delay occurred in isolation, without any concomitant impairment in motor function, cognition or social interaction. Therefore, the presence of language delay “only” was mutually exclusive with the presence of global developmental delay.

* 1 = present, 0 = absent

*Significant language delay:* the language delay was deemed to be “significant” if the impairment in language was a salient feature of the child’s phenotype, or if the language delay was classified as “severe” or “profound” according to the Bayley-III/GMDS-ER/ASQ report. Children with significant language delay as per the above definition generally showcased zero to five words. As an example, children from the cohort with Rett Syndrome were often non-verbal and met this criteria.

* 1 = present, 0 = absent

*Severity of developmental delay:* it was difficult to objectively determine the severity of developmental delay, since it was inherently defined during a period where achievement of milestones was incomplete and standardized testing could not be reliably performed. Where available, the grading indicated in the Bayley-III/GMDS-ER/ASQ report was taken as a reliable measure of severity. Where developmental tools had not been used, a descriptive impression of severity was formed by considering the child’s developmental delay in the context of social, practical and conceptual function. Social interaction was considered on a scale from mildly immature interactions, to moderately impaired capacity for relationships and communication, to a markedly severe impairment in understanding gestures and social cues. Practical skills varied from requiring mild support to achieve age appropriate goals, to moderately impaired skills requiring rigorous teaching and rehabilitation with allied health, to severe impairment where a high level of individual support was required for all activities of daily living. Conceptual thinking was assessed as mild difficulties with abstract thinking and executive function, to moderate impairment in learning and planning, to severe limitations in memory, problem solving, and goal directed behavior. Overall, if the child performed at a level less than 33% of biological age, the severity was rated as severe. If the child performed between 33% and 66% of biological age, the severity was rated as moderate. If the child performed at greater than 66% of biological age but still lagged significantly behind expected milestones, the severity was rated as mild.

* 1 = mild, 2 = moderate, 3 = severe/profound

*Autism spectrum disorder:* defined within the framework of the DSM-V criteria. The diagnostic criteria for ASD included significant impairment in social and emotional reciprocation, the presence of repetitive and stereotyped behaviours, fixated interests or preoccupations, and hyper-reactivity to sensory stimulation. Autism spectrum disorder was considered present when the child had been assessed in a neurodevelopmental clinic and deemed to meet the criteria of the DSM-V as outlined above.

* ASD: 1 = present, 0 = absent

*Intellectual disability:* this diagnosis was generally reserved for children over the age of 5 who experienced challenges in “conceptual, social and practical domains” stemming from an impairment in cognitive function and flexibility, as per the DSM-V criteria. The presence of intellectual disability was primarily gathered from placement of the child in an IM or IO classroom, or in a special education school. Where testing of IQ was available, children were also classified as having intellectual disability if they scored less than 70. Many of the children in the cohort had also been assessed for intellectual disability through formal testing using the “Wechsler Preschool and Primary Scale of Intelligence, 4th Edition (WPPSI)”, “Differential Ability Scales (DAS)”, and “Vineland Adaptive Behaviour Scales, 3rd Edition (Vineland-3)”. A diagnosis of intellectual disability was accepted in a child below the age of 5 if they had undergone testing with one of these tools, as these children had not yet received school placement.

* 1 = present, 0 = absent

*Severity of intellectual disability:* the severity of intellectual disability was dictated by the type of classroom placement. Children in an IM class were categorized as mild intellectual disability, those in an IO class were categorized as moderate intellectual disability, while placement in a special needs school was taken as evidence for severe or profound intellectual disability. Where available, the results of testing with WPPSI/DAS/Vineland-3 was used in rating the severity of intellectual disability, and overrode the severity indicated by school placement. Grading of severity was also corroborated by IQ testing where available, with 50-70 indicating mild intellectual disability, 35-49 indicating moderate intellectual disability, and less than 35 indicating severe or profound intellectual disability.

* Mild/moderate/severe: 1 = present, 0 = absent

*Cortical visual impairment:* defined as vision loss that was presumed secondary to a defect in the visual cortex, posterior visual tracts or areas involved in visual processing. There may or may not have been a history of hypoxic brain injury, cerebral malformation, head injury or perinatal infection. The diagnosis was made by exclusion through ophthalmological assessment to eliminate other anatomical, ocular or refractive causes of visual deficit. Conditions that were ruled out prior to the diagnosis of cortical visual impairment included hyperopia, myopia, amblyopia, anisometropia, astigmatism, strabismus and congenital cataracts.

* 1 = present, 0 = absent

*Sensorineural hearing impairment:* defined as hearing loss secondary to a defect of the inner ear apparatus or cochlear nerve. In the present cohort, this was most often idiopathic or hereditary in nature. Nevertheless, the potential for other causes was appreciated, such as perinatal exposure to viruses, bacteria or aminoglycoside and platinum-based drugs. It was diagnosed when other conductive causes of hearing loss had been excluded, such as ear wax, otitis externa, otitis media, otitis media with effusion, cholesteatoma or otosclerosis.

* 1 = present, 0 = absent

*Dysmorphism:* defined as any distinctive physical or structural characteristic suggestive of an underlying congenital defect or genetic syndrome. It included features such as hypertelorism, epicanthal folds, idiosyncratic shape of nose or upper lip, and abnormal philtrum length. Particular care was taken to identify the presence of dysmorphism through discussion between the data collector and the respective neurologist who had seen the patient, since it was often difficult to ascertain from the written notes. It was accepted that the treating neurologists had varying expertise in the assessment of dysmorphology, and the majority of patients were not seen by a geneticist. It is therefore likely that the presence of dysmorphism was under-reported in the present study.

* 1 = present, 0 = absent

*Neuro-cutaneous syndrome:* this included any of the conditions encompassed within the category of neurological disorders with concomitant dermatological manifestations, with or without other organ involvement. Examples included Neurofibromatosis Type 1 and 2 (NF1/NF2), Tuberous Sclerosis (TS) and Sturge-Weber Syndrome (SWS), a collection of syndromes with separate genetic causes, but with the common feature of defective ectodermal migration and differentiation. The diagnosis was made by the treating neurologist, having considered the diagnostic criteria set out in the literature for each respective syndrome, as outlined elsewhere [1].

* 1 = any neurocutaneous syndrome present, 0 = absent

*Microcephaly/Macrocephaly:* microcephaly was defined as head circumference persistently below the 3rd percentile for age, while macrocephaly was defined as head circumference persistently above the 97th percentile for age. Alternatively, this could equally be defined as head circumference more than 2 standard deviations below or above the mean respectively.

* 1 = microcephaly, 2 = macrocephaly, 0 = head circumference within normal limits

*Epilepsy:* this was defined according to the consensus document published by the International League Against Epilepsy (ILAE) in 2014 [2]. As mentioned in section 1.7, it defined epilepsy as a disease process in which a patient who has experienced at least one seizure demonstrates a predisposition to further seizure activity. The criteria for diagnosis included two unprovoked seizures separated by 24 hours, or a single unprovoked seizure with estimated recurrence risk higher than 60%, or the presence of a known epilepsy syndrome. In cases where the data collector had reason to dispute the diagnosis of epilepsy based on the above definition, this was raised with the treating neurologist and the history of seizure activity was revisited, with a thorough examination of medical records to resolve any conflicts. The treating neurologist ultimately determined whether the patient met the criteria for a firm diagnosis of epilepsy based on clinical judgement and results of EEG testing or neuroimaging. In order to classify the type of epilepsy, the most recent documents published by the ILAE in 2017 were used as a guide to describe seizure semiology. The following definitions are based on these position papers regarding epilepsy classifications [3, 4].

* 1 = present, 0 = absent

*Focal epilepsy:* defined by the presence of seizures in which the initial clinical features or EEG findings indicated a focal pattern of onset. The underlying epileptic activity was known or presumed to originate within one hemisphere of the brain. The presence of focal epileptiform discharges on interictal EEG was taken as evidence for focal epilepsy. Focal epileptic seizures were subdivided into those with preserved awareness and those with impaired awareness, although both were statistically captured within this single data point. Concluding the presence of focal seizures was easily justified when there was a focal motor pattern of onset, since the external physical expression of the seizure was apparent to the examiner or witness. In contrast, the presence of focal seizures in the context of non-motor symptoms was harder to elucidate. It was accepted that the presence of focal seizures could often be inferred by matching seizure semiology with epileptic patterns in the literature, which were known to be indicative of focal epilepsy. A common example is the presence of déjà vu which is then proceeded by lip smacking and loss of awareness, a known focal seizure based on the literature despite the absence of typically “focal” behavioural symptoms. In addition, many patients experienced seizures, which were initially focal but subsequently progressed to generalized tonic-clonic activity. These “focal to bilateral tonic-clonic” seizures were classified within this category of focal epilepsy, since they reflected propagation of the seizure to bilateral hemispheric networks, rather than reflecting an actual generalized pattern of onset.

* 1 = present, 0 = absent

*Generalized epilepsy:* defined by the presence of seizures in which the initial clinical features or EEG findings indicated a generalized pattern of onset. The underlying epileptic activity was believed to arise from, or rapidly engage, network in both hemispheres of the brain. The presence of classical generalized spike and wave activity on interictal EEG was taken as evidence for generalized epilepsy. Patients with generalized motor seizures and generalized absence seizures were all captured within this single data point. The discrete epilepsy syndromes, such as Childhood Absence Epilepsy, Juvenile Absence Epilepsy, Juvenile Myoclonic Epilepsy and Generalized Tonic-Clonic Seizures alone, were all appropriately classified as generalized epilepsy. It was appreciated that patients, such as those with Lennox-Gastaut or Dravet Syndrome, could manifest both focal and generalized seizures on separate occasions, in keeping with the classification system proposed by the ILAE. It was also appreciated that some syndromes such as West Syndrome, also known as infantile spasms, were often classified as having “unknown” onset. For the purposes of the present study, patients with West Syndrome were classified into focal or generalized epilepsy based on the unilateral or bilateral distribution of epileptiform discharges on individual EEG testing.

* 1 = present, 0 = absent

*Myoclonic semiology:* defined as brief involuntary jerking or twitching movements in one or more muscle groups during seizure activity. This seizure type could be seen in various epilepsy syndromes, such as Juvenile Myoclonic Epilepsy or Myoclonic Atonic Epilepsy (Doose Syndrome), but also in the context of severe hypoxic brain injury. It was deemed to be present if “myoclonic”, “twitching” and “jerking” were noted as consistent descriptors of seizure semiology in the patient’s medical records, and was confirmed with the treating neurologist.

* 1 = present, 0 = absent

*Tonic semiology:* defined as involuntary rigid contraction of extensor muscle groups, usually lasting for less than one minute. It was deemed to be present if “tonic” was noted as a consistent descriptor of seizure semiology in the patient’s medical records, and was confirmed with the treating neurologist.

* 1 = present, 0 = absent

*Status epilepticus:* defined as a continuous clinical seizure lasting for greater than 5 minutes in duration. This was counted in the data if the patient suffered even a single episode of status epilepticus as per the above definition.

* 1 = present, 0 = absent

*Epileptic encephalopathy:* this was deemed to be present if the severity of seizure activity caused stagnation or regression in the child’s development. The presence of an epileptic encephalopathy was also supported by a progression in the child’s development or behaviour with improved seizure control. Notable examples of patients who were counted as exhibiting an epileptic encephalopathy were those with West Syndrome and Continuous Spike and Wave during Sleep (CSWS). The presence of an epileptic encephalopathy was confirmed with the treating neurologist.

* 1 = present, 0 = absent

*Medically refractory seizures:* for the purposes of the present study, this was defined as the presence of at least one seizure per month for a period of 18 months, despite the use of at least two different anti-epileptic drugs which were tolerated by the patient and appropriately chosen for the specific seizure type [5].

* 1 = present, 0 = absent

*Ataxia or cerebellar syndrome:* this category encompassed the vast array of acquired, hereditary and idiopathic cerebellar pathologies that presented with axial or appendicular ataxia. This included cerebellar hypoplasia or atrophy, clinically significant cerebellar malformations, genetic conditions such as Friedreich ataxia and the spinocerebellar ataxias, and cerebellar neoplasms to name a few. In order to meet the criteria for a cerebellar cause of ataxia, patients had to report a history of clinically significant ataxia, with genuine cerebellar signs on clinical examination. Supporting evidence from the medical records, in the form of further genetic testing or MRI reports of cerebellar pathology, was sought wherever available. Developmental dyspraxia did not meet the criteria.

* 1 = present, 0 = absent

*Movement disorder:* defined as a neurological disease presenting with abnormal involuntary movements, impaired execution of voluntary movements, or inappropriate timing of a normal movement. The pathology was known or presumed to involve networks in subcortical structures such as the basal ganglia, as well as the cerebellum. If a patient demonstrated impaired control of movement due to pathology in the primary motor cortex, spinal cord, anterior horn cells, peripheral nerves, neuromuscular junction, or muscle fibers, they were not designated as having a movement disorder. The pathology needed to arise from circuits upstream to the final motor outflow in order to meet the criteria of a movement disorder. Therefore, patients with dyskinetic cerebral palsy, demonstrating choreoathetoid or dystonic movements secondary to basal ganglia injury during early development, were counted as having a movement disorder. In order to comprehensively characterize movement disorder phenomenology, the dyskinetic movement disorders were subdivided into tic disorders, chorea, dystonia, myoclonus and tremor, as defined below. Patients with hypokinetic phenomenology were also categorized within the overarching group of movement disorders, however this comprised a very small minority of the cohort.

* 1 = present, 0 = absent

*Tourette syndrome:* A tic is defined as a sudden involuntary movement, behaviour or vocalization which is stereotyped and repetitive in nature and often preceded by a rising urge to perform the tic itself. In contrast to other movement disorders, tics can be suppressed for a period of time, prior to the expression of a rebound tic due to overwhelming inner discomfort. Tourette syndrome was deemed to be present if diagnosed by the treating neurologist, in accordance with diagnostic criteria in the literature. As per the Tourette Syndrome Classification Study Group and DSM-V, this required the onset of motor and vocal tics prior to the age of 18, and a waxing and waning course with persistence of tics for more than 1 year.

* 1 = present, 0 = absent

*Other tic disorder:* defined as the presence of “Transient Tic Disorder”, “Provisional Tic Disorder”, “Chronic Motor or Phonic Tic Disorder”, or “Tic Disorder, Not Otherwise Specified”, as diagnosed by the treating neurologist in accordance with DSM-V criteria. This essentially incorporated tic disorders apart from Tourette syndrome.

* 1 = present, 0 = absent

*Chorea:* deemed to be present when the patient exhibited intrusive jerky movements which were continually changing in rate and direction, manifesting unpredictably in different muscle groups with a non-rhythmical and pervasive course. If there was a flowing or connected quality to the movement, then it was described as choreoathetoid. The presence of chorea was established by the treating neurologist.

* 1 = present, 0 = absent

*Dystonia:* defined in accordance with the consensus paper published by the Movement Disorder Society. Dystonia was characterized as an involuntary twisting or posturing movement caused by intermittent and sustained muscle contraction, often but not always provoked by voluntary initiation of muscle movement. In addition to the torsional component, a tremulous undertone can be displayed, and the phenomenology may be patterned and repetitive [6]. The presence of dystonia was affirmed by the treating neurologist.

* 1 = present, 0 = absent

*Myoclonus:* deemed to be present when the description of the movements employed adjectives such as “shock-like” or “jerky” or “twitching”. The diagnosis of myoclonus was confirmed with the treating neurologist and occurred in the absence of epileptic seizures with myoclonic semiology.

* 1 = present, 0 = absent

*Tremor:* defined in accordance with the consensus paper published by the Movement Disorder Society. Tremor was characterized as an “involuntary, rhythmic, oscillatory” movement, subdivided into both physiological and pathological forms [7]. Patients with pathological tremor, of known or presumed neurological cause, were included for the purposes of this study after confirmation with the treating neurologist. The presence of tremor secondary to non-neurological causes was actively excluded. The etiologies within this category included medications, toxins, heavy metal poisoning, or endocrine and metabolic disorders to name a few. The physiological forms of tremor of imperceptibly low amplitude and no clinical significance were obviously excluded for the purposes of this study.

* 1 = present, 0 = absent

*{Albanese, 2013 #97}Psychiatric co-morbidity:* the patient was considered to have a psychiatric illness if they were diagnosed with ADHD, depression, anxiety, obsessive compulsive disorder, psychosis or oppositional defiant disorder as per the following abbreviated definitions from the DSM-V. In each case, the diagnosis was made either by the treating neurologist, or paediatric psychiatrist where a referral had been made. If the patient did not strictly manifest one of the following diagnostic entities, but required pharmacological management for persistently severe behavioural disturbances after consultation with a paediatric psychiatrist, they were also included as having a psychiatric co-morbidity.

* 1 = present, 0 = absent

*ADHD:* a circular definition was used encompassing significant impairment in attention with hyperactivity or impulsivity, resulting in a negative impact on development or social function. The difficulty with maintaining focus contained elements of disorganization, and poor resilience in completing or sustaining given tasks. The hyperactivity and impulsivity manifested as excessive fidgeting or physical restlessness and acting with haste in the absence of due thought. In particular, these symptoms were required to permeate across multiple social settings, such as school and home.

* 1 = present, 0 = absent

*Depression:* for the purposes of the present study, major depression was the only disorder considered from the vast umbrella of depressive illnesses. As per the DSM-V, a child was considered to suffer from major depression if they had anhedonia or irritable and cranky mood in association with at least three other melancholic symptoms over a 2 week period, including insomnia, low appetite, psychomotor retardation, fatigue, poor concentration or suicidal ideation.

* 1 = present, 0 = absent

*Anxiety:* for the purposes of the present study, non-specific pathological generalized anxiety was the only clinical entity considered from the vast umbrella of anxiety disorders. It was considered to be present if the patient significantly distressed by feelings of anxiety on most days for longer than 6 months, across multiple social settings, and with the associated need for constant reassurance. This was substantiated by the presence of symptoms such as irritability, restlessness, poor concentration and difficulty with sleep. The presence of anxiety was confirmed by treating neurologist or paediatric psychiatrist where referral was made.

* 1 = present, 0 = absent

*Obsessive compulsive disorder:* defined as the presence of obsessions and compulsions which caused significant distress and functional impairment, or if the behaviours were time consuming to perform and therefore causing debilitation. These came in the form of intrusive and recurrent thought processes which triggered the individual to perform a stereotyped action in order to “neutralize” the obsessive thought and transiently relieve the inner sense of anguish.

* 1 = present, 0 = absent

*Psychosis:* a broad definition was used which encompassed any clinical entity presenting with delusions, auditory or visual hallucinations, formal thought disorder, grossly abnormal behaviour or catatonia.

* 1 = present, 0 = absent

*Oppositional defiant disorder:* indicated by the display of angry, defiant or malicious behaviour targeted towards individuals who were not siblings for a period of greater than 6 months. The conduct exhibited was unexpected or excessive with respect to the social predicament, and consequently impacted negatively on those who experienced the behaviour. Conversely, the behaviour caused significant personal distress to the patient from a developmental or educational perspective.

* 1 = present, 0 = absent

*Hypotonia:* deemed to be present when persistently reduced tone in axial or appendicular musculature was prominent on physical examination and documented on more than 2 sequential progress notes in the patient’s medical records.

* 1 = present, 0 = absent

*Hypertonia:* deemed to be present when persistently increased tone in axial or appendicular musculature was prominent on physical examination and documented on more than 2 sequential progress notes in the patient’s medical records.

* 1 = present, 0 = absent

*Spasticity:* deemed to be present when a velocity dependent increase in tone was prominent on physical examination and documented on more than 2 sequential progress notes in the patient’s medical records.

* 1 = present, 0 = absent

*Cerebral palsy:* defined as an enduring yet non-progressive disorder of movement and posture. There was not a requirement for a history or radiological evidence of brain injury for a diagnosis of cerebral palsy- the diagnosis was made on clinical grounds. The phenotype commonly included comorbidities such as developmental delay, intellectual disability, epilepsy, movement disorders, behavioral issues, abnormalities in tone and secondary musculoskeletal issues. The diagnosis of cerebral palsy was confirmed with the treating neurologist, and patients were classified according to the distribution of spasticity and dominant clinical phenotype. With respect to distribution, patients were described as either diplegic, hemiplegic, or quadriplegic. In terms of dominant phenotype, patients were described as having spastic, ataxic, dyskinetic, hypotonic or mixed cerebral palsy.

* 1 = present, 0 = absent
* Type: 1 = hemiplegic, 2= diplegic, 3 = quadriplegic, 4 = dyskinetic, 5 = ataxic, 6 = unclear/mixed, 7 = hypotonic

*Weakness:* defined as the presence of reduced muscle strength, with resultant impact on activity and movement, caused by a myopathy or neuropathy as per the definitions below.

* 1 = present, 0 = absent

*Myopathy:* defined as the presence of functional weakness caused by any congenital or hereditary pathology present primarily within muscle, diagnosed either through clinical history and examination or with the help of muscle biopsy. This incorporated congenital conditions such as Duchenne and Becker Muscular Dystrophies, glycogen storage diseases such as Pompe’s disease, and myoglobinurias such as McArdle’s disease, whilst excluding toxic and medication related acquired myopathies.

* 1 = present, 0 = absent

*Neuropathy:* defined as the presence of functional weakness caused by any congenital or hereditary pathology present primarily within peripheral nerves, diagnosed either through clinical history and examination, nerve conduction studies or with the help of nerve biopsy. This primarily represented the hereditary motor and sensory neuropathies classified under Charcot Marie Tooth disease. However, hereditary neuropathies selective to motor, sensory or autonomic nerves were also included when manifesting clinically significant impairments. Toxic and medication related acquired neuropathies were excluded.

* 1 = present, 0 = absent

*Spastic hereditary paraplegia:* this comprised the diverse group of inherited disorders characterized by gait disturbance, caused by a combination of spasticity and weakness of the lower limbs. The presence of hereditary spastic paraplegia was confirmed by the treating neurologist and diagnosed based on family history, examination and genetic testing where available.

* 1 = present, 0 = absent

*Malformation on MRI:* a broad definition was used which encompassed any anatomic derangement of the brain, presumed to arise from abnormal neurogenesis during the fetal period, secondary to both genetic and environmental etiologies. This was ascertained from the description of “malformation” on the MRI report, or when deemed to be present by the treating neurologist. Examples of malformations included hemimegalencephaly, lissencephaly, polymicrogyria and schizencephaly.

* 1 = present, 0 = absent

*Dysplasia on MRI:* a broad definition was used which encompassed any dysplasia of cortical architecture, or any MRI abnormality which indicated the presence of dysplastic cells. This was predominantly ascertained from the MRI report. The type of focal cortical dysplasia (such as 1a, 1b, 2a and so on) was noted where histo-pathology studies had been performed.

* 1 = present, 0 = absent

**References**

1. Little, H., D. Kamat, and L. Sivaswamy, *Common Neurocutaneous Syndromes.* Pediatric Annals, 2015. **44**(11): p. 496-498, 500-504.

2. Fisher, R.S., et al., *A practical clinical definition of epilepsy.* Epilepsia, 2014. **55**(4): p. 475-482.

3. Scheffer, I.E., et al., *ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology.* Epilepsia, 2017. **58**(4): p. 512-521.

4. Fisher, R.S., et al., *Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology.* Epilepsia, 2017. **58**(4): p. 522-530.

5. Berg, A.T., et al., *How long does it take for epilepsy to become intractable? A prospective investigation.* Annals of Neurology, 2006. **60**(1): p. 73-79.

6. Albanese, A., et al., *Phenomenology and classification of dystonia: A consensus update.* Movement Disorders, 2013. **28**(7): p. 863-873.

7. Bhatia, K.P., et al., *Consensus Statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society.* Movement Disorders, 2018. **33**(1): p. 75-87.