Cerebral palsy not always what it seems

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Cerebral palsy (CP) is an umbrella term that defines a group of non-progressive, but often changing, syndromes of motor impairment secondary to lesions or anomalies of the brain arising in the early stages of its development.\(^1\)\(^2\) The characteristic clinical feature that is common to all CP syndromes is the presence of pyramidal or extrapyramidal signs. CP is neither a specific disease nor a pathological or aetiological entity, and importantly the term CP does not—and should not—necessarily imply or identify a specific cause. The prevalence of CP ranges from 1.5 to 2.5 per 1000 live births, with the risk highest among very preterm and low birthweight babies. However, the majority of children with CP are born at or near term gestation. Causes of CP include perinatal hypoxic-ischaemic encephalopathy, intra- or periventricular haemorrhage, cerebral dysgenesis, and intracranial infection. The CP syndromes may be classified by the predominant type of motor disturbance, including, for example, diplegia, tetraplegia, hemiplegia, dyskinesia, and ataxia, although frequently the overall clinical picture is not always pure. Finally, the aetiologies for these different syndromes tend to be quite distinct.

Once a diagnosis of CP has been made on the basis of the child’s symptoms and signs, each child should undergo appropriate evaluation and investigation to try and establish a cause and specifically to determine whether it is of prenatal, perinatal, or postnatal origin. Investigation is indicated even when there has been evidence of a preceding neurological event during the perinatal period or infancy, because some of these children may have an underlying neurological or metabolic disorder which may have made them more vulnerable to the stresses of delivery and extrauterine life. Finally, it is important that all children with a diagnosis of CP should be followed up, and when no obvious cause has been identified or there is any evidence of regression, children should be referred to a paediatric neurologist. A number of neurodegenerative, including metabolic and genetic disorders may present with similar symptoms and signs. Some of these disorders which are slowly progressive are more likely to be misdiagnosed as CP. Individually these disorders may be rare, but collectively they are not. It is important that these disorders are correctly diagnosed as early as possible for a number of reasons. Firstly, some may be treatable; secondly, the family can be provided with more accurate information regarding the prognosis; and finally, genetic counselling may be offered, including, where appropriate, prenatal testing. Table 1 lists the more common diseases which have not infrequently been misdiagnosed as CP, both in our experience and that of others. This is not a comprehensive list.

## Apparent muscle weakness

MUSCLE weakness does not occur in CP, but not uncommonly the profound hypotonia seen in children with CP in the first year of life is misinterpreted as weakness. Genuine muscle weakness implies a peripheral neuromuscular component including an anterior horn cell disorder, a peripheral neuropathy or a myopathy, or a defect in neuromuscular transmission. However, children aged 2 years and over with evolving CP will also have clonus and exaggerated deep tendon reflexes (DTRs) in the lower limbs. Some disorders, including mitochondrial leucodystrophy, infantile neuroaxonal...
dystrophy, and the pontocerebellar atrophies, frequently show simultaneous central and peripheral nervous system involvement, and may lead to an initial diagnosis of CP.

Duchenne muscular dystrophy (DMD) usually presents with delayed independent walking and an awkward and often tiptoe gait. This presentation, particularly if accompanied by non-motor developmental delay, as occurs in ataxia, particularly if accompanied by non-

peripheral nervous system involvement, and may frequently show simultaneous central and peripheral neuropathy. Signs and symptoms are often present in other family members and should be specifically sought. Inheritance may be X linked, autosomal dominant (commonly in the “pure” form) or recessive, and spontaneous mutations may also occur.

With predominant diplegia or tetraplegia

Arginase deficiency is an autosomal recessive disorder of the urea cycle, resulting in argininaemia and intermittent moderately raised plasma ammonia concentrations. Clinically, patients present with loss of motor and cognitive skills, progressive spastic diplegia or tetraplegia, and deficient linear growth. Seizures may also occur. The diagnosis is confirmed by raised arginine concentrations in plasma amino acid analysis, or by measuring arginase in cultured skin fibroblasts.

Metachromatic leucodystrophy as the classic late infantile form presents with delay or deterioration in walking and progressive ataxia by 3 years of age. Eventually, the child becomes tetraplegic and often dies before 7 years of age. Optic atrophy and greyish discolouration of the retina and macula, sometimes with a central red spot, develop. The juvenile form presents between the ages of 4 and 12 years, often with deterioration in school performance and unusual behaviour. There is clumsiness of gait and ataxia, which progresses to paraplegia within a year of onset. Diagnosis is made by showing increased excretion of urinary sulphatide and reduced or absent activity of the blood lysosomal enzyme arylsulphatase A.

Adrenoleucodystrophy is an X linked cerebral demyelinating disease with adrenal insufficiency, presenting between 5 and 10 years of age with intellectual decline, visual impairment, and spasticity, often with ataxia and, less commonly, seizures.

The juvenile/adult form of the condition, adrenomyeloneuropathy, presents with stiffness or “clumsiness” in the legs, which progresses to spastic paraplegia over five to 15 years. The diagnosis may be suggested by abnormal brain magnetic resonance imaging (MRI) and confirmed by finding raised concentrations of very long chain fatty acids in blood or cultured fibroblasts, or by DNA analysis.

Hereditary progressive spastic paraplegia, a genetically heterogeneous degenerative disorder of the spinal cord and brain, is characterised by a slowly progressive spasticity affecting the legs, late sphincter involvement, and occasional subtle cognitive impairment. There is a variable age of onset and the condition may be “pure” or “complicated”, the latter showing a number of neurological or non-neurological features including dementia, seizures, ataxia, optic atrophy, cutaneous lesions, and peripheral neuropathy. Signs and symptoms are often present in other family members and should be specifically sought. Inheritance may be X linked, autosomal dominant (commonly in the “pure” form) or recessive, and spontaneous mutations may also occur.

With significant dystonia/involuntary movements

Dystonia and involuntary movements (specifically choreoathetosis) are not as common in CP as is generally believed. If present in CP, these features typically occur following a short but profound period of hypotension and hypoxia in the perinatal period.

Dopa responsive dystonia (DRD) may mimic athetoid or dyskinetic CP. Dystonia, usually affecting the legs, which usually worsens throughout the day, occurs in early childhood or, less commonly, in adolescence. The abnormal gait is often quite bizarre and may initially be interpreted as psychogenic in origin or “hysterical”. The gait disturbance usually shows a dramatic and sustained response to small doses of levodopa. A trial of levodopa should be used in all children who present with dystonia. In the differential diagnosis, Wilson disease should be considered when orofacial dystonia accompanies limb dystonia in children over 8 years of age, and idiopathic torsion dystonia when the dystonia is asymmetric and develops after 10 years of age.

Glutaric aciduria type I, an autosomal recessive condition, results from a failure to metabolise lysine, hydroxylysine, and tryptophan. The disease usually presents in late infancy, either with mild, global developmental delay and a relative macrocephaly or with an acute encephalopathy in the first two years of life. Some children present later with dystonia and choreoathetosis. Diagnosis is confirmed by showing raised concentrations of glutaric acid and 3-hydroxyglutaric acid on urine organic acid analysis. Occasionally these concentrations may be low and the diagnosis can be confirmed by measuring activity of the enzyme glutaryl CoA dehydrogenase in cultured fibroblasts. Dietary and pharmacological treatment may modify the course of the disease.

Pyruvate dehydrogenase complex deficiency is a common cause of lactic acidosis; in most cases
it is caused by mutations in the X linked gene coding for the Ela subunit of this mitochondrial enzyme complex. Pyruvate and alanine concentrations may also be raised in urine, blood, and cerebrospinal fluid. The clinical presentation is variable. The most severe presentation is of infantile acidosis, resulting in death by 6 months of age. Patients with less notable but more chronic lactic acidosis, often have clinical and neuropathological features of Leigh syndrome. They may have dystonia, spastic tetraparesis, microcephaly, mental retardation, and epilepsy. MRI commonly shows symmetrical lesions in the basal ganglia, thalami, and brain stem. Children may show rapid deterioration or episodic stepwise deterioration following infections. Leigh syndrome may be caused by abnormalities in the mitochondrial respiratory chain enzymes, including pyruvate carboxylase deficiency, biotinidase deficiency, fumarase deficiency, and 3-methylglutaconic aciduria.

Lesch–Nyhan disease is an X linked recessive condition presenting in the first year of life. Following normal or near normal development for the first six months, children then rapidly develop spasticity, choreoathetosis, and notable mental retardation, epilepsy, and dystonia. The diagnosis may be confirmed by showing the characteristic stereotyped and often continuous hand function. The latter results in the characteristic triad of self-injury, trismus, and hyperekplexia. Partial deficiency of the enzyme results in a milder clinical phenotype.

Rett syndrome, a slowly progressive disorder of development in girls, is characterised by progressive microcephaly, mental retardation, spastic tetraparesis, opisthotonic dystonia, gastroesophageal reflux, and recurrent episodes of aspiration pneumonia. The diagnosis is confirmed by enzyme assay in leucocytes or cultured fibroblasts.

With significant ataxia

Ataxia telangiectasia (AT) presents in the first three years of life with repeated respiratory tract infections and is accompanied by progressive spasticity and dysthria. The characteristic conjunctival and ear telangiectases develop later (after the age of 4 years). AT may be diagnosed by high concentrations of serum α-fetoprotein, low serum IgA concentrations, or by DNA analysis. Chronic/adult GM 1 gangliosidosis storage disease may present with progressive cerebellar dystonia, ataxia, myoclonus, and spasticity. Intellectual impairment may be mild and dystonia may be a prominent feature. Fundoscopy may reveal cherry red spots. Diagnosis may be confirmed by showing reduced β galactosidase in leucocytes.

X linked spinocerebellar ataxia may present with spastic diplegia; additional clinical features may include nystagmus, ataxia, pyramidal signs, dysthria, and learning difficulties.

Pontocerebellar atrophies/hypoplasias are a group of disorders which may present at any stage of the disease. The diagnosis is made by showing notably delayed cerebral myelination on MRI, abnormal visual evoked potentials, or, more definitively, by DNA analysis.

3-Methylglutaconic aciduria is an autosomal recessive disorder characterised by increased urinary excretion of 3-methylglutaric and 3-methylglutconic acids. It most commonly affects families of Iraqi–Jewish origin, and is manifest by involuntary movements, ataxia, spasticity, and, less commonly, optic atrophy.

Partial deficiency of the enzyme results in a milder clinical phenotype. Inspiratory stridor is a relatively common and additional characteristic feature and may occur at any stage of the disease. The nystagmus tends to resolve in later childhood. Diagnosis is made by showing notably delayed cerebral myelination on MRI, abnormal visual evoked potentials, or, more definitively, by DNA analysis.

Pelizaeus–Merzbacher disease is a slowly progressive X linked leucodystrophy with mixed pyramidal and extrapyramidal manifestations, resulting from a deficiency of a myelin protein, proteolipid protein. It presents in the first year (often months) of life with characteristic pendular nystagmus (never seen in CP), notable involuntary movements (choreoathetosis), a spastic tetraparesis, and relatively intact intellect, although the latter may be difficult to appreciate because of the involuntary movements of the limbs and orofacial muscles. Niemann–Pick disease type C is an autosomal recessive condition which presents neurologically between the ages of 2 and 12 years, with
tremor, clumsiness, ataxia, poor concentration, vertical supranuclear ophthalmpoplegia, dysarthria, and dystonia. Seizures may develop and the neurological dysfunction is progressive. Ultimately, there is complete loss of vertical eye movements involving both upward and downward gaze, which, occurring on a background of progressive neurological deterioration is almost pathognomonic of this disorder. The initial presentation is commonly in the first year of life, with failure to thrive and hepatosplenomegaly. The diagnosis is established by showing sea blue histiocytes in bone marrow or by impaired cholesterol esterification on cultured fibroblasts and the positive filpin test for accumulation of free cholesterol.

Mitochondrial cytopathies, specifically caused by the 8993 mutation causing neurogenic muscle weakness, ataxia, and retinitis pigmentosa (NARP) may also be misdiagnosed as “familial CP”; CP caused by a perinatal insult such as periventricular leucomalacia or hypoxic encephalopathy rarely recurs in families. “Familial CP” should always raise the possibility of an underlying genetic disorder, including a number of metabolic diseases.

With significant bulbar and oromotor dysfunction

Bulbar and oromotor dysfunction, including speech and feeding difficulties, are not uncommon in CP, but tend to be less severe than the more prominent motor and mobility difficulties.

Worster-Drought syndrome (also called the bilateral perisylvian or opercular syndrome) describes a supranuclear (pseudobulbar) palsy that presents with sucking and swallowing difficulties, excessive salivation, severe dysarthria, and an exaggerated jaw jerk. Children also usually show either a mild spastic diplegia or hemiplegia, variable cognitive and behavioural impairment, and epilepsy. The condition may be congenital or acquired; MRI usually shows abnormalities of the opercular cortex, with dysgenesis (including defects of neuronal migration) of the perisylvian region in the congenital form.

Conclusions

Cerebral palsy is a neurological syndrome and refers to a combination of signs and symptoms; it is not a disease. It encompasses a group of non-progressive, but often changing, motor impairment syndromes secondary to lesions or anomalies of the brain, arising in the early stages of its development. A number of symptoms and signs are common to both CP and neurodegenerative/metabolic disorders, particularly in infancy and early childhood. All children with features of CP should be carefully evaluated for an underlying cause, particularly in the following situations:

- Absence of a definite preceding perinatal insult
- Presence of a positive family history of “cerebral palsy”
- Occurrence of developmental regression (loss of abilities)

Presence of oculomotor abnormalities, involuntary movements, ataxia, muscle atrophy, or sensory loss.

Investigation should then be determined on an individual basis, depending on the history and clinical findings, and looking particularly for those metabolic disorders that can be identified by blood and urine amino acid analysis, urine organic acid analysis, and measurement of white blood cell enzymes. However, it is the authors’ belief that MRI of the brain and brain stem should be undertaken in all children with features of CP. Ideally, MRI should be performed at 2–3 years of age, when it is easier to assess cerebral myelination or identify any subtle cerebral dysgenesis, although earlier brain imaging may be appropriate in children who have congenital microcephaly, who are dysmorphic, or who have evidence of either a congenital or early onset hemiplegia. Neuroimaging may also provide radiological evidence to support a history of a perinatal neurological insult, or it may suggest an alternative cause for the child’s neurological findings.

Finally, there should be a low threshold for referring children to a paediatric neurologist or a clinical geneticist, or both if appropriate. This should be determined by the clinical history and examination findings and the experience of the general paediatrician. Evidence of a family history of “cerebral palsy”, progressive neurological signs, and/or regression are absolute indications for a paediatric neurological assessment.


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