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REVIEW ARTICLE

Diagnosing cerebral palsy in full-term infants

Catherine Morgan,[1,2] Michael Fahey,[3] Bithi Roy[1,4,5] and Iona Novak[1,2]

[1]School of Medicine, Paediatrics and Child Health, [2]Cerebral Palsy Alliance, School of Child and Adolescent Health, University of Sydney, [4]School of Medicine, University of Notre Dame, [5]Special Care Nursery, Mater Hospital Sydney, Sydney, New South Wales and [3]Department of Paediatrics, Monash University, Melbourne, Victoria, Australia

Abstract: More than 50% of infants with cerebral palsy (CP) are born at or near term, with the vast majority having pre- or perinatally acquired CP. While some have a clinical history predictive of CP, such as neonatal encephalopathy or neonatal stroke, others have no readily identifiable risk factors. Paediatricians are often required to discriminate generalised motor delay from a variety of other diagnoses, including CP. This paper outlines known causal pathways to CP in term-born infants with a focus on differential diagnosis. Early and accurate diagnosis is important as it allows prompt access to early intervention during the critical periods of brain development. A combination of clinical history taking, standard clinical examination, neuroimaging and genetic testing should be started at the time of referral. Attention to the investigation of common comorbidities of CP, including feeding and sleep difficulties, and referral to early intervention are recommended.

Key words: cerebral palsy; genetic testing; neuroimaging; perinatally acquired cerebral palsy; preterm infants.

Cerebral palsy (CP) is the most common physical disability of childhood and is a heterogeneous condition resulting from damage to the developing brain. The causal pathways to CP are many, and not all are known. However, the consensus definition describes CP as a group of disorders of movement due to a non-progressive lesion/abnormality that occurred in the developing brain.[1]

The prevalence of CP in Australia is 1 in 500 live births, and data from the Australian Cerebral Palsy Register indicate that the rate of CP appears to be declining. Furthermore, there are fewer children with severe motor impairment and co-occurring intellectual disability or epilepsy.[2] Most CP originates in the pre- or perinatal period, with only 8% of cases attributed to post-natal causes. In fact, 57% of children with CP are born at term age, and the majority has no immediately identifiable risk factors for CP.[3] This lack of clinical history often leads to late diagnosis and delayed referral for intervention. A Danish register study found that ambulant children with CP are the latest to be diagnosed, particularly those with bilateral spastic CP who are a mean age of 23.9 months at diagnosis.[4] In contrast, non-ambulant children typically receive their diagnosis by 6 months of age. A retrospective study showed that referral for intervention is often delayed until the second year of life unless the child is a neonatal intensive care unit (NICU) graduate.[5] Late access to early intervention is detrimental, resulting in lost opportunities during the critical window for neuroplasticity.[6] Now that 60% of children with CP walk independently and a further 11% use walking devices,[7] there is an ethical imperative to ensure access to CP-specific intervention as early as possible. Children with milder CP are the most responsive to early motor training, and earlier diagnosis is crucial to optimise their outcomes and prevent complications.

Paediatricians are often required to distinguish between CP and other causes of motor delay, and this task can be difficult in infancy without a suspicious clinical history and no overt neurological signs, such as spasticity or retained reflexes. Paediatricians may adopt a 'wait and see' approach to avoid falsely labelling children and to placate parents. However, this can result in poorer parental mental health[8] as well as delayed intervention. This paper seeks to update first-contact practitioners about how to diagnose CP in infants born at term. Case studies and a diagnostic algorithm are provided (Table 1 and Fig. 1).

Key Points

1 Cerebral palsy is more common in full-term than preterm infants and can be challenging to diagnose in infants without pronounced risk factors.
2 Early diagnosis and intervention improve outcomes, especially for those with mild cerebral palsy.
3 There is increasing evidence of a genetic contribution.

Correspondence: Dr Catherine Morgan, Cerebral Palsy Alliance, School of Child and Adolescent Health, University of Sydney, 88 Mallett St, Camperdown, NSW 2050, Australia; email: cmorgan@cerebralpalsy.org.au

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Step 1: Take a Thorough Clinical History

For some infants presenting to a paediatrician with atypical motor development, a brief clinical history may highlight well-known risk factors. However, many of these children at first have a seemingly healthy pregnancy and neonatal history, but with detailed history taking, risk factors for CP can be identified.[10] Full-term infants can have all sub-types of CP but usually have more severe motor impairments than preterm infants.[10] Risk factors can occur at multiple time epochs, and therefore, taking a good clinical history is essential. Systematic review evidence indicates that preconception

Table 1 Clinical scenarios

Case studies: Diagnosis and management				
Clinical history	Presenting issues	Investigations	Treatments	Outcome
Seven-month term baby with neonatal encephalopathy, Sarnat 3	• Sleep problems: Wakes hourly at night, no day sleep • Unsettled all day, needs to be held	• Sleep paediatrician resulting in diagnosis of GORD • OT consult	• High-dose Losec and Zantac • Sleep hygiene recommendations	• Sleep through the night in 10 days + day sleeps • Rapid developmental progress • CP: GMFCS III, normal IQ
Nine-month term baby, HIE, not cooled. MRI on day 7, damage to deep grey matter. Abnormal GMs and HINE score < 40 at 3 months. Epilepsy and spasms managed with Clobazam and Keppra	• Sleep disorder: Waking six times at night • Food refusal at 9 months due to pain although on recommended reflux meds	• Gastroenterologist referral	• Temporary NG tube • High-dose reflux meds	• Reduced pain • Increased caloric intake • Improved sleep and learning • CP: GMFCS V
Five-month-old term baby with uncomplicated birth and pregnancy history. Developmental milestones and growth all within normal limits	• Asymmetry of hand use, with right hand often closed	• HINE assessment with a score of 59 and 7 asymmetries	• Neurology review • MRI under GA reveals large area of encephalomalacia in LMCA territory	• Referred to physiotherapy and occupational therapy • CP: Hemiplegia, GMFCS 1, MACS 2
Five-month-old baby born at 37 weeks, BW 2450 g. Required neonatal resuscitation and had Apgar of 3 at 1 min. Spent 3 weeks in SCN. Normal CUS and MRI. Hip dysplasia treated with Pavlik harness	• Developmental delay, referred by allied health clinicians	• Neuro exam: Full head lag • Microarray chromosome analysis was normal • 12 months: Developed seizures • Repeat MRI at 12 months revealed white matter injury	• Neurology review • Medications for seizures • Early intervention	• At 2 years, sibling also presented with seizures and developmental delay • Genomic analysis demonstrated pathogenic mutation in CANA1A in both siblings

BW, birth weight; CP, cerebral palsy; CUS, cranial ultrasound; GMs, general movements; GMFCS, Gross Motor Classification Scale; HINE, Hammersmith infant neurological examination; MACS, Manual Ability Classification Scale; MRI, magnetic resonance imaging; NG, nasogastric; OT, occupational therapy; SCN, special care nursery.

risks include: a history of previous miscarriage, stillbirth and neonatal death; maternal age (both young and older); race; low socioeconomic status; maternal history of thyroid disease; or coagulation, disorders or seizures. Antenatal risk factors include: poly- or oligohydramnios; haemorrhage; infection; pre-eclampsia; placental abnormalities; major and minor birth defects; small and large for gestational age; and plurality, multiple pregnancy and gender. Intrapartum risk factors include: length of labour; prolonged rupture of membranes; meconium-stained liquor; breech presentation; caesarean section; instrumented delivery; cord around the neck; cord prolapse; placental abruption; uterine rupture; haemorrhage; or birth asphyxia. Neonatal risk factors include: seizures; respiratory distress; hypoglycaemia; jaundice and infection.[10]

High risk for CP

Neonatal encephalopathy

Infants born at term with neonatal encephalopathy (NE) account for 25% of term CP.[11] These infants typically require resuscitation at birth. Therapeutic hypothermia is now standard of care for infants with moderate to severe signs and symptoms.[12] Cooling is recognised as a successful preventative measure for preventing death and reducing the incidence and severity of CP.[12] Best-practice diagnostics include brain magnetic resonance imaging (MRI) with diffusion at days 7–10 of life. Infants with severe neonatal encephalopathy whose imaging reveals basal ganglia and thalamic injury most often have dyskinetic CP affecting all four limbs and trunk. These children are often diagnosed early due to tone problems affecting volitional movement and posture and are enrolled in follow-up programmes. Less severe NE is still a risk factor for CP, and these children often have co-occurring risk factors including congenital anomalies and growth restriction.[3] Most but not all children with dyskinetic CP are non-ambulant. The Australian Register indicates that 25% walk. Referral to early intervention is essential for optimising motor function but also for stimulating early cognitive and literacy development as many of these children have normal intelligence.

In contrast, if the infant has a seemingly normal birth history but has clinical signs of encephalopathy in the first year of life,

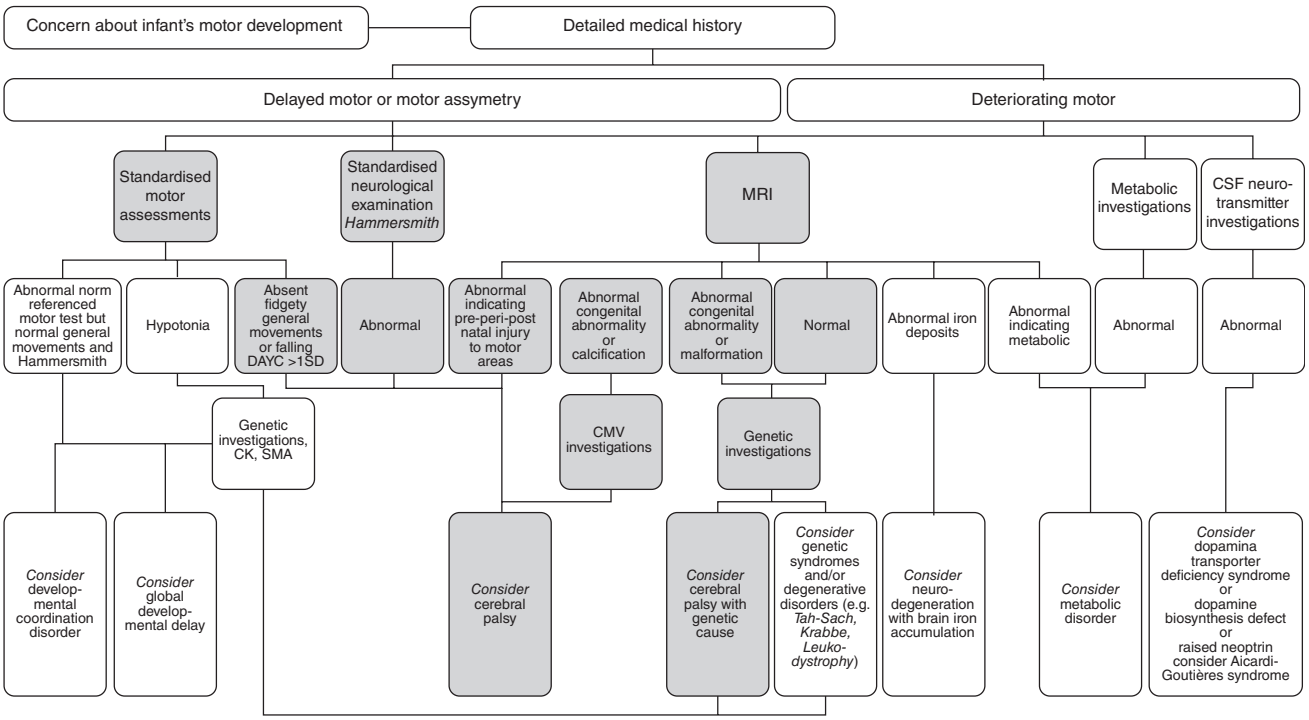

Fig. 1 Algorithm for differential diagnosis of term-born cerebral palsy. Note: This figure incorporates Kurian *et al*.'s[9] algorithmic decision-making support for the identification of dopamine transporter syndromes. CK, creatine kinase; CMV, cytomegalovirus; CSF, cerebrospinal fluid; DAYC, developmental assessment of young children; MRI, magnetic resonance imaging; SD, standard deviation; SMA, spinal muscular atrophy.

with the MRI showing calcification, consider testing for Aicardi–Goutières syndrome, with neurotransmitters. Aicardi–Goutières syndrome is an autosomal recessive encephalopathy presenting with acquired microcephaly, cerebral atrophy, cerebral calcifications, leukodystrophy, lymphocytosis and raised interferon-alpha cerebrospinal fluid levels.

Stroke

Perinatal stroke is the most common type of paediatric stroke and is the leading cause of post-natally acquired CP.[13] It may occur *in utero* from 22 weeks or up to a month after birth due to haemorrhage or ischaemia or a thromboembolic phenomenon.

Clinical signs of a perinatal stroke may be subtle and go unnoticed, although many present with neonatal seizures. Best practice diagnostics include placental pathology and MRI with diffusion to determine whether or not brain injury has occurred and whether the injury has affected the motor areas and tracts predicting CP. If clinical history and MRI are suggestive, these children can be enrolled into follow-up programmes with neonatology or neurology as children at high risk of CP. Some infants may present in the first few months of life with asymmetry of motor activity, most commonly in the upper limb. However, the asymmetry can also present later, after 6–9 months following cortical pruning and maladaptive response to injury – thus, early intervention is critical for the preservation and reorganisation of motor function. Single or multiple disabilities, such as hemiplegic CP, epilepsy, cognitive or behavioural disorders, may be present following perinatal stroke depending on the location of the lesion.[14–16]

Infants at the highest risk of CP are increasingly diagnosed early using the new international early diagnosis clinical practice guideline.[17]

Moderate risk for CP

Full-term infants at moderate risk of CP include those with congenital disabilities, septicaemia, meningitis, small for gestational age or growth-restricted infants and those who cannot sit by 9 months or who demonstrate early motor asymmetry. These children should be thoroughly screened as they are often late to be diagnosed and to receive intervention.[17] Sensitive and specific tools are described in the early diagnosis clinical practice guideline.[17]

Step 2: Organise Assessments

Neuroimaging

Brain MRI is commonly used to help establish a recognisable pattern that may contribute to an understanding of the likely aetiology in CP, and several systematic reviews associate patterns of MRI change with an estimated timing of damage.[18] These studies categorise changes into three major groups that broadly ascribe damage to different stages of gestation; these include those of abnormal brain development occurring mainly in the first and second trimesters and those with periventricular change relating to changes early in the third trimester in those with cortical or deep grey matter abnormalities, which are associated with

changes in the late third trimester. A possibly surprising result is the rate of malformations of cortical development, which occurs in approximately 10% of those with CP and is significantly over-represented in term compared to preterm children. Imaging is therefore recommended as part of the diagnostic workup for CP.[17]

It is important to remember that 9–16% of infants with CP have no detectable changes on MRI scanning.[19] Those with hypotonic or ataxic forms are over-represented in this group. Therefore, a normal MRI does not exclude the clinical diagnosis of CP.[19] The historical and clinical picture is important. Clinicians should be wary of progressive and/or treatable conditions such as dopa-responsive dystonia.[20] Furthermore, MRI can help with prognostication of motor severity and likelihood of co-occurring impairments, such as central vision impairment, that require specialist referrals for intervention. In contrast, cranial ultrasound is more useful in predicting CP in term than preterm infants. While some studies indicate that increased echogenicity in the basal ganglia is an indicator of risk, the value of cranial ultrasound is not established in prospective studies.[21]

Genetics testing

As many as one third of full-term children with CP lack traditional risk factors. In many of these, a genetic basis is suspected. Clues to a genetic contribution to the clinical syndrome of CP include dysmorphic features and a phenotype that does not 'fit' the history. A progressive condition is inconsistent with CP, although it may be difficult to identify if it evolves slowly. Population studies 25 years ago[22] demonstrated that one third of CP identified following term delivery were thought to be dysmorphic but did not have an immediately recognisable syndrome. The Australian authors postulated that these children might be more vulnerable to damage by comparatively minor hypoxic–ischaemic insult. These studies have been corroborated recently by CP registry data[23] where congenital abnormalities or intra-uterine growth restriction were identified in 48.6% of term or near-term singleton deliveries with CP. Of children with CP in this study, 15–40% were reported to have a major congenital abnormality compared to a national figure of 3.6%. There is an overlap between the phenotype of CP and syndromic diagnoses, and in these instances, there is an increasing role for genetic or genomic diagnosis.

Contemporary genetics studies identify increased *de novo* copy number variation rates in CP[24] in up to 20%.[25,26] Exome analysis can identify[27–29] further genomic abnormalities cohorts of CP. While some genes are novel, studies often ascribe a new role to a previously recognised gene. A genetic contribution may be present in as many as 34–45% of cases.[26] This yield may be increased by focusing on particular groups with a distinctive phenotype.

The hypotonic phenotype of CP is one where there may be particular interest from a genetic standpoint. Registry studies indicate that hypotonic CP is associated with an increased rate of mortality[30] and of autism.[31] Furthermore, this group has relatively higher rates of normal neuroimaging.[20] However, hypotonic CP is included as a registry field in only 54% of programmes surveyed and is not defined consistently.[32] Further work is needed to define the overlap in those with dysmorphic features and low tone. It is also apparent that there needs to be harmonisation between registries from different parts of the world regarding the terminology used.

Standardised motor/neurological examination

Standardised motor assessment should always form part of the diagnostic process for infants with motor delay or aberrant motor behaviours such as early handedness. Paediatric allied health clinicians can assist with this part of the diagnostic workup. Most commonly used assessment tools can discriminate between normal and abnormal motor performance but do not accurately discriminate between CP and motor delay.[33,34] Recent guidelines for the early detection of CP identify the most sensitive assessments for detecting CP:[17]

- Prechtl's qualitative assessment of general movements (GMA): The GMA assesses the spontaneous movement of infants and is scored using a 3–5 min video. Between 12 and 20 weeks post-term age, the GMA has the highest sensitivity and specificity for detecting CP with values of about 98% and 91%, respectively, during the fidgety period (9–20 weeks.) These values have also been confirmed in Australian settings, and GMA is now regarded as a standard assessment in high-risk populations.[35] Once volitional movements are more predominant around 5 months of age, general movements cannot be reliably tested.[36]
- Hammersmith Infant Neurological Examination: From 2 to 24 months, the Hammersmith Infant Neurological Examination is one of the most sensitive tools for detecting CP.[18] This scoreable neurological assessment can be easily used in the clinical setting and can be learned with minimal training. Optimal scores are defined with cut-off values for CP at 3, 6, 9 and 12 months,[37] and scores less than 40 strongly predict non-ambulant CP. In the case of suspected hemiplegia, it is important to document the number of asymmetries as mildly affected children may score in the optimal range.[38]

Assessments that focus on motor milestones are not reliable predictors of CP unless used longitudinally. The Developmental Assessment of Young Children, the Alberta Infant Motor Scale and the Neurological, Sensory, Motor, Developmental Assessment all have good sensitivity and specificity for CP when used over time.[39,40] It is important to note that some children with mild CP may have near normal milestone acquisition over the first year of life, especially those with mild hemiplegia. Some motor tests allow the fine motor component to be scored on the less affected side only, giving a false impression of 'normality'. It is therefore important to assess the quality of movement as well as the existence of asymmetry when parents express concern.

The age of the infant will determine the 'best practice' choice of assessments at initial presentation but always involves a combination of assessments to triangulate findings.

Step 3: Investigate Comorbidities

Comorbidities are common, particularly in severely affected children, and can be more disabling than the motor impairment.[41] Investigating and managing these comorbidities are necessary to optimise outcomes and prevent secondary impairments. Three in

4 experience chronic pain; 1 in 2 have an intellectual disability; 1 in 3 have a hip displacement; 1 in 4 cannot talk; 1 in 4 have epilepsy; 1 in 4 have a behaviour disorder; 1 in 4 have bladder control problems; 1 in 5 have a sleep disorder; 1 in 5 have sialorrhoea; 1 in 10 have vision impairments; 1 in 15 require tube feeding and 1 in 25 have hearing impairments.[41] The most common comorbidities in infants include: pain from reflux, constipation or involuntary postures arising from the movement disorder; sleep disorders from either unmanaged pain or apnoea or vision impairments affecting sleep onset; or seizures. Prophylactic hip X-rays to detect hip displacement should commence from 1 year of age. In the first year of life, regularly checking in with parents about the child's pain and sleep is an essential part of best practice care.

Summary

Paediatricians have an essential role to play in the early identification of full-term infants with CP, most of who will not have been under the care of a neonatologist. When an infant presents with atypical movement or motor development, it is important to take a thorough clinical history and conduct investigations using sensitive and specific tools. Neuroimaging and specific motor assessments are initially used to identify potential causes and probable severity. Genetics investigations might also be required if results are confounding. The term 'high risk of cerebral palsy' can be given before final confirmation of the diagnosis so that early intervention can begin. An early CP diagnosis enables diagnostic-specific early intervention. Investigations should be undertaken for concurrent impairments.

Multiple Choice Questions

1 What is the one most common comorbidity in severe cerebral palsy (CP)?
   a) Chronic pain
   b) Epilepsy
   c) Hip displacement
   d) Intellectual disability
   e) Sleep disorder

Answer: a. About 75% have chronic pain, compared with 25% with epilepsy, 33% with hip displacement, 50% with intellectual disability and 20% with a sleep disorder.

2 Which one form of CP is associated with autism?
   a) Ataxic
   b) Athetoid
   c) Dyskinetic
   d) Hypotonic
   e) Spastic diplegia

Answer: d. Hypotonic CP is associated with increased risk of autism and increased mortality.

3 Which one is the most common cause of post-natally acquired CP?
   a) Child abuse
   b) Congenital malformations
   c) Genetic
   d) Meningitis
   e) Perinatal stroke

Answer: e. Perinatal stroke due to haemorrhage or ischaemia or a thromboembolic phenomenon may occur *in utero* from 22 weeks and for up to a month after birth.

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