Cerebral palsy

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Abstract | Cerebral palsy is the most common cause of childhood-onset, lifelong physical disability in most countries, affecting about 1 in 500 neonates with an estimated prevalence of 17 million people worldwide. Cerebral palsy is not a disease entity in the traditional sense but a clinical description of children who share features of a non-progressive brain injury or lesion acquired during the antenatal, perinatal or early postnatal period. The clinical manifestations of cerebral palsy vary greatly in the type of movement disorder, the degree of functional ability and limitation and the affected parts of the body. There is currently no cure, but progress is being made in both the prevention and the amelioration of the brain injury. For example, administration of magnesium sulfate during premature labour and cooling of high-risk infants can reduce the rate and severity of cerebral palsy. Although the disorder affects individuals throughout their lifetime, most cerebral palsy research efforts and management strategies currently focus on the needs of children. Clinical management of children with cerebral palsy is directed towards maximizing function and participation in activities and minimizing the effects of the factors that can make the condition worse, such as epilepsy, feeding challenges, hip dislocation and scoliosis. These management strategies include enhancing neurological function during early development; managing medical co-morbidities, weakness and hypertonia; using rehabilitation technologies to enhance motor function; and preventing secondary musculoskeletal problems. Meeting the needs of people with cerebral palsy in resource-poor settings is particularly challenging.

The term cerebral palsy refers not to a specific disease entity, but rather to a group of conditions with variable severity that has certain developmental features in common. The formal definition, delineated by an international panel in the mid-2000s, is as follows: "Cerebral palsy describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication and behaviour, by epilepsy and by secondary musculoskeletal problems". The nuances of this definition are parsed in more detail elsewhere[1] (FIGS 1,2).

What links all people with cerebral palsy are the clinical and functional onset of symptoms in early development, the high probability that the symptoms have an effect on the whole life course and the current lack of a definitive cure. Almost all children with cerebral palsy survive to adulthood. In fact, survival rates among even the most functionally compromised young people with cerebral palsy have remarkably improved over the past few decades, as demonstrated by population-based data from the California Department of Developmental Services[2,3], but remain lower than typically developing controls.

Cerebral palsy has traditionally been identified as part of a spectrum of neurodisability, with the imperative to understand aetiological forces, potential primary prevention and early therapies that can mitigate the effects of brain impairment on function. However, given that cerebral palsy presents early in infancy and persists throughout an individual's lifetime, the disorder needs to be thought of and managed in the context of development, functioning and the family[4]. Interventions are necessary to promote and enhance child and family functioning and well-being to prevent secondary musculoskeletal impairments and to help families plot a successful life-course plan for their children (and themselves) in the face of developmental differences.

The past 25 years have been the most exciting and productive time in the field since William J. Little first described what we now call cerebral palsy[5]. However, despite neuroscientific breakthroughs described in

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this Primer, and discussed in detail elsewhere[6], many unanswered questions remain. Among the most compelling challenges for the twenty-first century is the need to chart and understand the life course of adults who have grown up with a 'children's condition' and whose adult lives remain affected by the condition[7]. Hopefully this Primer on cerebral palsy will begin a new and fruitful dialogue, and stimulate a new generation of young practitioners and scientists to work towards answers to these basic clinical and scientific issues.

Epidemiology

Cerebral palsy is the most common motor disability of childhood. Population-based registries of cerebral palsy, largely in Australia and Europe, have historically found cerebral palsy prevalence ranging from 1.5 to 2.5 per 1,000 live births[8]. However, recent studies in the United States[9], Taiwan[10] and Egypt[11] have found prevalence rates above 3 per 1,000 live births in people 4–48 years of age. The increased survival of very premature infants has contributed to a modest increase in the prevalence of cerebral palsy in developed countries over the final quarter of the twentieth century that now appears to be levelling off[12].

The earliest clinical description of children with cerebral palsy recognized that most patients had two factors in common: premature birth and difficult labour with neonatal asphyxia (or oxygen deprivation)[5]. Both factors were considered direct causes of cerebral palsy, but are now considered reflective of factors operating earlier in development[13]. Infants who experience fetal inflammation, for example, are more likely to be born prematurely and to develop cerebral palsy; fetal inflammation probably contributes independently to both outcomes[14]. Indeed, although newborns with Down syndrome are five-times more likely to experience birth depression, as indicated by a low (<6 out of 10 points) Apgar score (which evaluates the baby's condition based on skin colour, heart rate, reflexes, muscle tone and breathing rate and effort) 5 minutes after birth, we do not ascribe Down syndrome to birth asphyxia[15].

Preterm birth is the most important risk factor for cerebral palsy. Risk increases steadily with declining gestational age at birth, with a modest increase in risk already detectable as early as 38 weeks of gestation[16]. The risk in infants born before 28 weeks of gestation is approximately 50-times that of full-term births[17] (FIG. 3). Among premature births, the most important risk factor is evidence of white matter damage on cranial ultrasonography or other brain-imaging modalities. Infants with evidence of persistent damage, such as single or multiple brain lesions (cystic or cavitary) or ventriculomegaly (dilatation of the lateral brain ventricles), have a roughly 50% risk of developing cerebral palsy[18]. Perinatal factors that have been associated with the development of cerebral palsy in premature infants include: chorioamnionitis (intra-amniotic infection) or other evidence of perinatal inflammation, especially when sustained postnatally[19]; transient hypothyroxinaemia (low maternal thyroid hormone levels)[20]; and hypocapnoea (reduced carbon dioxide levels, which can induce cerebral vasoconstriction) in association with mechanical ventilation[21]. Some of these factors are also associated with the risk of developing white matter damage, but whether all of these associations are directly causal is unclear. The finding that intra-uterine growth retardation and postnatal inflammation have additive effects on the risk of cerebral palsy development in premature infants indicates that combinations of biological processes could also be involved in acquiring this condition[22]. Several recent trials have demonstrated that cerebral palsy is reduced by approximately 30% in premature infants whose mothers received magnesium sulfate during labour (see below)[23–26].

In full-term infants, who account for the majority of cases of cerebral palsy (FIG. 3), signs of birth depression, such as low Apgar score, also correlate with an increased risk of developing cerebral palsy[27]. However, in the absence of birth depression, many other complications of labour probably do not raise the risk of cerebral palsy[28]. Imprecision regarding the proportion of cerebral palsy that is causally attributable to birth asphyxia in part reflects the difficulty of rigorously defining birth asphyxia[29], but only ≤10% of children who develop cerebral palsy clearly experienced major birth asphyxia. Various perinatal abnormalities often attributed to birth asphyxia — such as meconium passage, need for caesarean section, neonatal seizures and respiratory difficulties after birth — are correlated with cerebral palsy[30], but may reflect other underlying biological processes that occur earlier in development. Birth defects outside of the brain, such as cardiac and skeletal abnormalities[31], are found with much greater frequency in cerebral palsy. A most important recent advance in cerebral palsy prevention is the discovery that 72 hours of brain or body cooling in full-term infants with birth asphyxia will reduce the prevalence of cerebral palsy[32].

Other factors that are associated with a higher risk of cerebral palsy at term include placental abnormalities and fetal growth retardation[33]. Neonatal

hyperbilirubinaemia (excessive levels of bilirubin in the blood owing to red blood cell breakdown) can cause dyskinetic cerebral palsy at any gestational age, but is now fortunately very rare in developed countries as a result of preventive interventions, including exchange blood transfusion, phototherapy and, most importantly, Rh_o(D) immune globulin therapy (that is, maternal anti-RhD immunoglobulin treatment to prevent Rhesus disease in the fetus or newborn)[34].

Approximately 10–15% of children with cerebral palsy have a brain malformation other than a brain lesion, which usually requires neuroimaging to detect[35]. A small percentage of cerebral palsy (<5%) in full-term infants is a consequence of perinatal ischaemic stroke; this is mainly associated with hemiplegic cerebral palsy in which only one side of the body is affected[36].

Given that socioeconomic status is strongly associated with preterm birth and low birth weight, one might

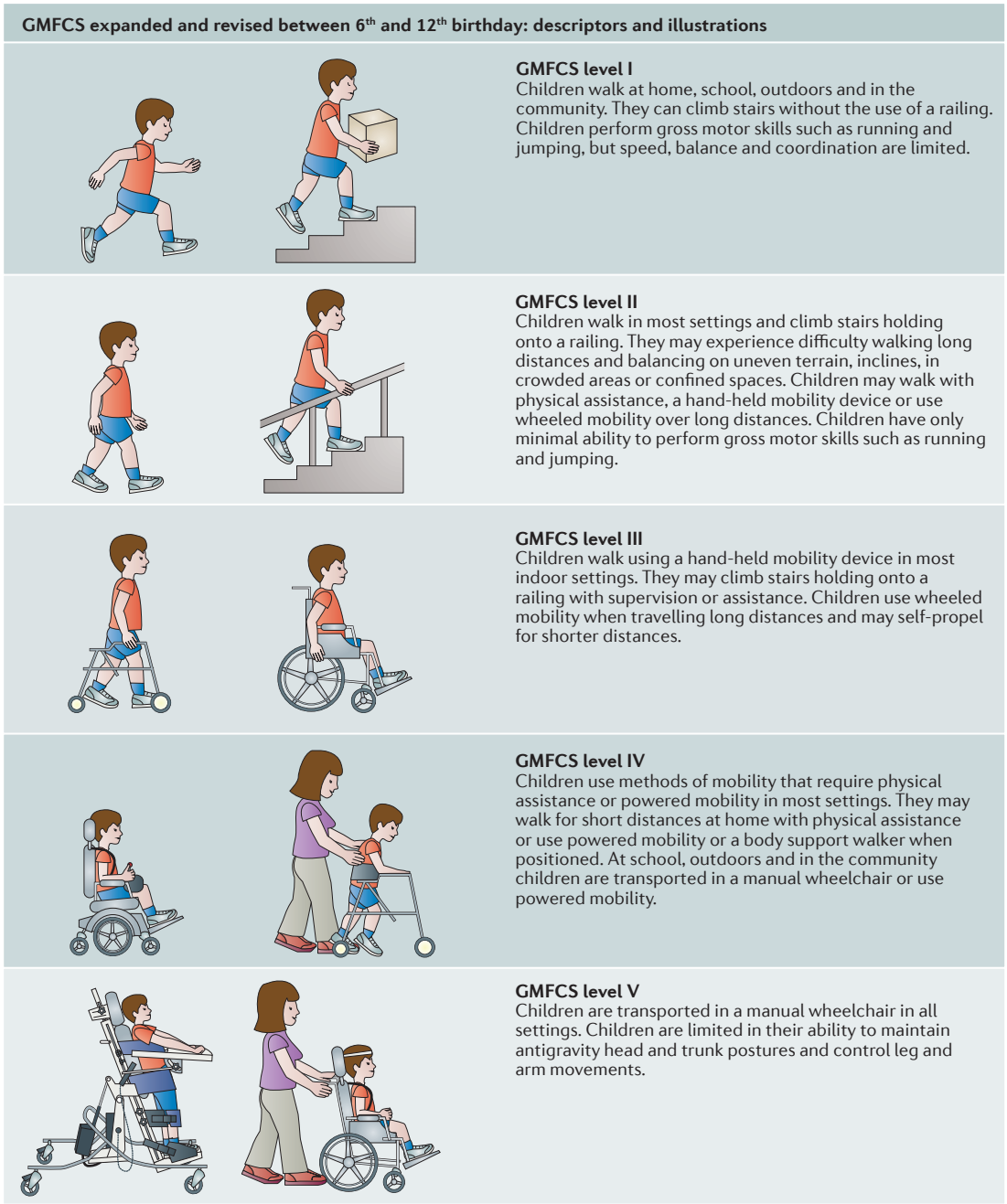

Figure 1 | **Gross Motor Function Classification System expanded and revised for children with cerebral palsy, 6–12 years of age.** The Gross Motor Function Classification System (GMFCS) has become the gold standard to classify motor function in children with cerebral palsy. The GMFCS is an ordinal classification in which different descriptors are used according to the age of the child. The descriptors for children 6–12 years of age are shown. GMFCS has been shown to be valid, reliable, stable and predictive of long-term gross motor function. The descriptors were devised by Palisano *et al.*[284,285]. Images are courtesy of B. Reid, A. Harvey and H.K.G., The Royal Children's Hospital, Melbourne, Victoria, Australia.

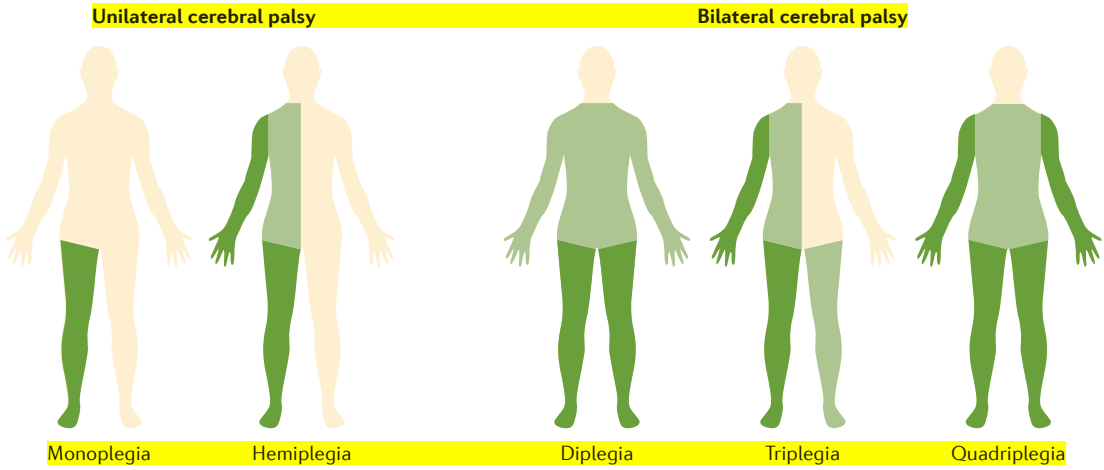

Figure 2 | **Topographical description in cerebral palsy: unilateral and bilateral cerebral palsy.** In monoplegia, one limb is affected and it is more often the lower limb. In hemiplegia, one side of the body is affected and the upper limb is usually more affected than the lower limb. These topographical types are equivalent to the Surveillance of Cerebral Palsy Europe (SCPE) unilateral cerebral palsy[121]. In diplegia, all limbs are affected, but the lower limbs are much more affected than the upper limbs, which frequently only show fine motor impairment. In triplegia, the usual pattern is unilateral upper limb involvement and bilateral (asymmetrical) lower limb involvement. The lower limb is invariably more affected on the same side as the upper limb involvement. In quadriplegia, all four limbs and the trunk are involved. Synonyms for quadriplegia include tetraplegia or 'whole-body involvement'. Diplegia, triplegia and quadriplegia are covered by the term bilateral cerebral palsy according to SCPE terminology.

expect that cerebral palsy shows a similar gradient, and it does seem to[37,38]. The prevalence of cerebral palsy seems to be higher in African-American infants in the United States, which may be explained by the higher rate of preterm birth in African-American women[39].

Of seven population-based studies of the epidemiology of cerebral palsy in low-income and middle-income countries reviewed by Durkin[40], one study showed much lower prevalence than in developing countries, two were in the same range and four showed higher prevalences, ranging from 4.4 to 10 per 1,000 live births or children. This observation hints to an increased risk of cerebral palsy in low-income and middle-income countries versus high-income countries despite the fact that many who experience perinatal brain-damaging events that might lead to cerebral palsy in developing countries do not survive infancy. In some regions of the world, children may be born with a neurological syndrome that strongly resembles spastic diplegia — a type of cerebral palsy — due to severe iodine deficiency[41]. Neonatal jaundice caused by high levels of bilirubin remains a major risk factor for cerebral palsy in developing countries, as is perinatal infection.

Little is known of the distinct epidemiology of the different subtypes of cerebral palsy. Hemiplegic cerebral palsy, as noted above, at times represents the effects of a perinatal ischaemic stroke, but can occur in premature infants who have unilateral porencephalic cavities (or cysts in the cerebrum filled with cerebrospinal fluid) following white matter damage. Spastic diplegia, which is usually accompanied by periventricular white matter loss, is linked to both preterm birth and fetal growth retardation at term. The combination of spastic quadriplegia with dyskinesia in term infants has been associated with severe birth asphyxia. Dyskinesia accompanied by sensorineural hearing loss is the form of cerebral palsy most often seen with kernicterus (a form of brain damage due to high levels of bilirubin). The rarest form of cerebral palsy, ataxic cerebral palsy, sometimes indicates the presence of a cerebellar malformation.

Mechanisms/pathophysiology

Cerebral palsy is a clinical entity that implies much heterogeneity in terms of aetiology and pathophysiology[1]. Our understanding of the pathways leading to cerebral palsy has gained much from epidemiological, neuroimaging and post-mortem studies and animal models. However, a comprehensive understanding of the mechanisms that underlie the many features and profound phenotypic variations of cerebral palsy to enable specific strategies for management and primary and secondary prevention is yet to emerge.

Brain lesions

Characteristics. In approximately 90% of cases, cerebral palsy results from destructive processes that injure healthy brain tissue rather than from abnormalities in brain development[42] (FIG. 4). Hypoxia and ischaemia have traditionally been proposed as causes of brain injury. Pathological and imaging studies of cerebral palsy have demonstrated varying combinations of lesions in the cerebral cortex, the hemispheric white matter, the basal ganglia and the cerebellum[43]. The stage of brain maturation during which pathogenetic events occur defines the type and site of lesions, as well as the specific response to injury.

Early in maturation (that is, in the fetus and the preterm infant) blood vessels in the brain have limited capacity for dilatation, which enhances ischaemia and

leads to diffuse injury. Diffuse injury during the second trimester of pregnancy leads to liquefaction necrosis (a type of necrosis that transforms tissue into a viscous liquid mass), resulting in porencephalic cysts[44]. The astrocytic response to injury (including biochemical activity and morphological changes), which might lead to gliosis, is limited during the second trimester of pregnancy (<15% of the level observed in the mature brain) and gradually increases during development. Astrocytic response leads to cysts with increasing components of astroglial proliferation and septation observed for insults up to the neonatal period and astrogliosis without cysts for lesions sustained later[44].

The localization of brain lesions following diffuse insult markedly varies with gestational age. In preterm infants, deep periventricular white matter, which is a site of active proliferation of oligodendrocytes, is the most vulnerable. Maturation-dependent metabolic and molecular factors further enhance the susceptibility of the periventricular white matter in the preterm brain[45,46]. Consequently, periventricular leukomalacia (necrosis of white matter near the lateral ventricles) is the characteristic lesion pattern seen in cerebral palsy associated with preterm birth; it can be diffuse, focal or multifocal, cystic or non-cystic. By contrast, insults occurring in full-term infants primarily affect the cerebral cortex and underlying subcortical and periventricular white matter as a result of other maturation-dependent factors[45] and probably factors affecting vascular supply with changes in intervascular boundary (watershed) zones (that is, border-zone regions in the brain supplied by major cerebral arteries where blood supply is slightly reduced).

Phenotypical variability. Cerebral palsy is associated with various motor defects, which largely depend on the location of the brain lesion. Disruption of cortico–striatal–thalamic–cortical and cortico–cerebellar–cortical networks impairs motor planning, coordination, muscle strength regulation, motor learning and fine motor skills. Additional disruption of descending motor pathways that project to the brainstem and spinal relays, and retention of circuits that normally disappear with maturation result in persistent or poorly inhibited 'primitive' reflexes, abnormal organization of movement and posture, hyperactive reflexes and abnormal muscle tone, including spasticity. The motor impairments, with poor motor repertoire, hypertonia, progressive muscle changes related to neuronal, nutritional and mechanical factors, lead to musculoskeletal deformities.

Pathogenesis of brain lesions. The link between perinatal respiratory difficulties leading to hypoxia or ischaemia and cerebral palsy has been recognized clinically since the original description by Little[5], and it has served to design various animal models since the 1950s. Given that birth asphyxia does not account for the majority of cases of cerebral palsy, other mechanisms must play a part.

Brain injury in response to hypoxia or ischaemia is suggested to involve several events, including cellular energy depletion, excitotoxicity (that is, damage or death of nerve cells owing to excessive stimulation by neurotransmitters, particularly glutamate) and oxidative stress; oxidative stress leads to mitochondrial failure that further exacerbates this energy depletion. Ultimately, neurons and glial cells undergo apoptosis or necrosis (FIG. 5).

ATP depletion caused by mitochondrial failure disrupts cellular ATP-dependent processes, which may result in cell death. Among ATP-dependent processes, Na^+/K^+-ATPase disruption alters neuronal membrane potential, contributing to glutamatergic *N*-methyl-D-aspartate (NMDA) receptor-mediated excitotoxicity through massive Ca^{2+} influx into the cytoplasm, leading to necrosis and apoptosis[43,47]. Understanding this pathway has led to the study of the potential neuroprotective effects of agents that block NMDA receptors, including magnesium sulfate[23].

Intracytoplasmic Ca^{2+} overload induces necrosis and apoptosis by inducing oxidative stress. Activation of Ca^{2+}-dependent oxidases and inhibition of antioxidant activities[48] generate excess reactive oxygen species that affect mitochondrial function, which further increases the rate of reactive oxygen species production, ultimately leading to cell death. This effect is particularly marked early in brain maturation (second trimester) owing to the limited efficiency of scavenging systems[43]. This notion has led to the development of neuroprotective strategies based on free-radical-scavenging agents, such as melatonin[49]. In addition, the use of high oxygen concentrations in resuscitation approaches in neonatal asphyxia are contraindicated on the basis of studies in animals[50] and those showing adverse clinical outcome in humans[51].

Various insults, not just hypoxia and ischaemia, can lead to necrosis and/or apoptosis. Necrosis occurs as an immediate response to injury and typically results in focal injury that involves nonspecific cell-type death. Conversely, apoptosis is more protracted, usually more diffuse and cell specific — preferentially targeting

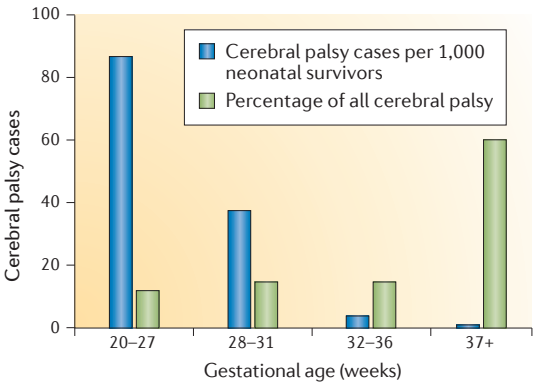

Figure 3 | **Association between gestational age and the prevalence of cerebral palsy.** The 'paradox' is the very strong relationship between prematurity and risk of cerebral palsy versus the fact that most patients with cerebral palsy are born at term. Graph is based on data described in REF. 286.

pre-oligodendrocytes if the process is triggered in the brain. These characteristics of necrosis and apoptosis are reflected in patterns of white matter injury, which occur in at-term birth but are typically associated with pre-term birth[52]. Necrosis results in focal lesions that can be microscopic and evolve into gliosis (a nonspecific reaction of glial cells in response to injury that involves proliferation and hypertrophy), which is the predominant neuropathological finding in non-cystic periventricular leukomalacia. Less commonly, necrosis can lead to macroscopic cysts, for example, in cystic periventricular leukomalacia. The consequence of pre-oligodendrocyte apoptosis is hypomyelination. The pathways underlying these two cell death mechanisms offer potential targets for anti-necrotic or anti-apoptotic intervention[53].

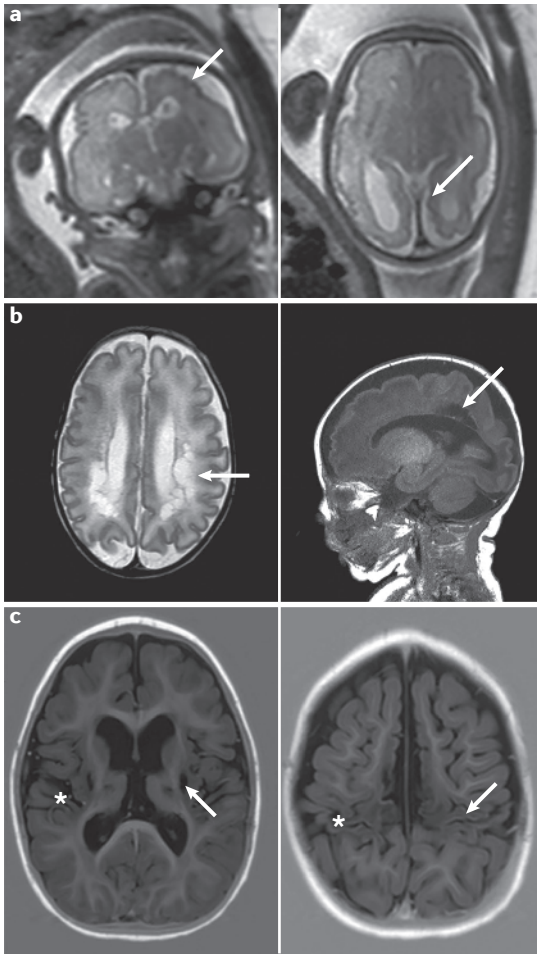

Figure 4 | **Brain lesions in cerebral palsy. a** | Coronal (left) and axial (right) MRI scans at 32 weeks of gestation showing frontal lobe hypoplasia and polymicrogyria (arrow). The child developed severe bilateral spastic cerebral palsy (Gross Motor Function Classification System (GMFCS) level V). **b** | Axial (left) and sagittal (right) MRI (spin echo T2 and spin echo T1) scans obtained at 5 weeks in an infant born preterm (at 30 weeks of gestation). Images show cystic periventricular leukomalacia (arrow). The child developed severe bilateral spastic cerebral palsy (GMFCS level IV). **c** | Axial MRI (inversion recovery) images obtained at 3 years in a child with birth asphyxia at term, showing cortico–subcortical atrophy particularly marked in the perirolandic region (asterisk) and porencephalic cysts in the basal ganglia bilaterally (arrow). The child had severe mixed-type (spastic and dyskinetic) cerebral palsy (GMFCS level V). Images are courtesy of C. Christophe, Université Libre de Bruxelles, Brussels, Belgium, and M. Cassart, Ixelles Hospital, Brussels, Belgium.

Animal findings[43] suggest that the hypoxia–ischaemia hypothesis has the most relevance in the case of perinatal asphyxia in the full-term newborn, as opposed to pre-term newborns. At term, the vulnerability to a deficit in oxygen supply is higher than earlier in development. The highest metabolic requirements involve the grey matter, chiefly the basal ganglia, the thalamus and parts of the cerebral cortex. This metabolic demand is reflected in patterns of brain damage at term, with lesions to these structures and clinical signs of dyskinetic, spastic or mixed-type cerebral palsy. The notion of failure to meet the metabolic demand has been the focus of studies of animal models preparing the development of therapeutic hypothermia as the standard of care for full-term newborns with moderate or severe perinatal asphyxia[54].

In addition to these advances, much progress has been achieved based on clinical, epidemiological, experimental and pathological evidence of the implication of maternal and neonatal inflammation, whether infective or non-infective. The inflammatory pathway may also be a target of strategic therapies. Although the role of pro-inflammatory cytokines has mostly been studied in relation to periventricular leukomalacia and cerebral palsy associated with preterm birth, hypoxia–ischaemia at term also triggers the release of pro-inflammatory cytokines, mostly from astrocytes, leading to damage to neighbouring neurons. Indeed, inflammation has been suggested to be a final pathway in cerebral palsy pathogenesis common to hypoxia–ischaemia, brain infection, systemic maternal infection, or fetal or infant infection, and other conditions in which they are produced, including trauma, inflammation and autoimmunity[43]. These pro-inflammatory cytokines can induce the expression of adhesion molecules in brain parenchymal and vascular endothelial cells and can promote microglial activation and demyelination[55].

Secondary nerve maturation. The clinical symptomatology can be directly attributable to brain abnormalities or can occur in the course of development as a secondary consequence of activity limitations[1] during critical periods for activity-dependent and use-dependent plasticity. For example, in addition to motor impairment components ascribed to lesions along motor pathways, restricted sensorimotor experience (less neural stimulation owing to fewer or less-complex movements) impedes motor learning. Similarly, visual impairment can result from a combination of lesions to visual pathways and poor perceptual development experiences. These reinforcing attributes would be a strong argument for early intervention as a means of secondary prevention.

The developmental aspect of cerebral palsy implies a special focus on neuroplasticity. For example, the

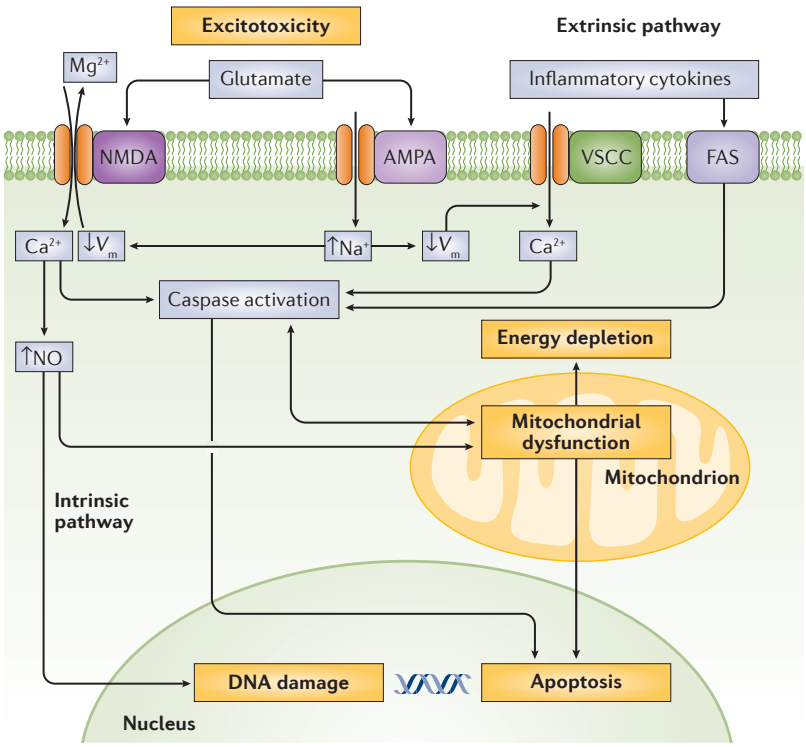

Figure 5 | **Cell death signalling pathways.** Extrinsic and intrinsic cell death pathways activate common signalling networks within the mitochondrion and the nucleus. The extrinsic pathway is triggered by inflammatory cytokines binding to the cell surface to activate FAS (also known as TNFRSF6 or CD95) death receptors and *N*-methyl-D-aspartate (NMDA) receptor-activated excitotoxic action of glutamate. The intrinsic pathway is activated when signals released from within stressed mitochondria activate caspase-mediated and non-caspase-mediated cell death pathways within the nucleus. Mitochondria that are exposed to caspase-induced stress can release cytochrome *c* (caspase-mediated cell death) or apoptosis-inducing factor, which activates DNA fragmentation directly (non-caspase pathway). DNA breaks can be mediated by free radicals, such as nitric oxide (NO). V_m, membrane potential; VSCC, voltage-sensitive Ca^{2+} channel.

corticospinal tract from the less affected hemisphere can project bilaterally on spinal relays, particularly if damage occurred before 24 weeks of gestation[56]. Evidence from adaptive, partially compensatory plasticity driven by experience has influenced therapy programmes. Moreover, a lack of physiological pruning (that is, postnatal synapse elimination) of early neural connectivity can also impair motor control[57].

Among non-motor features, mechanisms underlying visual dysfunction have been well documented. Cerebral visual impairment, in particular attentional and perceptual deficits, has been related to lesions in ventral and dorsal streams[58]. The ventral stream leads from the occipital lobe through to the temporal lobe to process object identification and recognition; the dorsal stream terminates in the parietal lobe and is involved in processing the spatial location of an object relative to the viewer. These notions have become an important focus in management strategies. Similarly, there has been increasing interest in understanding other cognitive outcomes, with respect to, for example, communication, executive functions and arithmetic performance.

Skeletal muscle in cerebral palsy

Whereas cerebral palsy results from a primary injury in the central nervous system (CNS), clinical symptoms are observed in the peripheral neuromuscular system — skeletal muscles in particular. Indeed, muscle contractures, defined as limited joint movement that results from high passive muscle force, are common complications of cerebral palsy. Our understanding of the tissue-level adaptations — both functional and structural — in muscle contractures has dramatically improved in recent years.

Muscle and muscle fibres. Muscles from children with cerebral palsy are shorter and smaller and contain fibres of reduced diameter[59] (FIG. 6). Human skeletal muscles have different fibre-type distributions, meaning that muscles contain a mixture of fast-contracting and slow-contracting fibres[60]. Numerous descriptions of altered fibre-type distribution in cerebral palsy muscle have been reported[61]. However, some studies report fibre transformation in the slow-to-fast direction, whereas others report fibre transformation from the fast-to-slow direction. These inconsistent results are mainly because fibre type varies widely among the muscles sampled and sampling is extremely unreliable[62]. Overall, it seems that muscle fibre types are not uniformly affected by cerebral palsy. Thus, decreased fibre diameter, which leads to a muscle with smaller force-generating area[63], partially explains decreased strength in these children.

Sarcomere length and number changes. The most dramatic and unprecedented change that has been documented in the muscles of children with fixed contractures (that is, contractures that are present all the time, even when the muscle is relaxed) are the sarcomeres that are almost twice the normal length and fewer in number. The sarcomere — the functional unit of contraction of the muscle[64] — is highly lengthened even though the muscle is highly shortened[65] (FIG. 6a,b). These long sarcomeres in short muscles are a paradoxical muscle adaptation that has now been observed in contractures due to cerebral palsy in wrist flexors[66], hamstrings[67] and plantar flexors[68]. The extremely long sarcomeres are thought to generate relatively low active force and could also contribute to the weakness observed in children with cerebral palsy in addition to the size changes mentioned above[67]. Longer sarcomere lengths are also associated with high passive muscle forces (that is, muscle force borne by the tissue in the absence of any neural activation). To date, the mechanistic basis for the extremely long sarcomeres observed in individuals with cerebral palsy is not known. However, the transcriptional profiling studies and tissue-level analyses described below may provide insights.

Mechanical properties of muscles. The most consistent mechanical change observed in the muscles of patients with cerebral palsy is hypertrophy of the extracellular matrix (ECM), which leads to increased muscle stiffness[67,69]. Increased amounts of ECM can be quantified

in various ways[70], with the most common being biochemical measurement of collagen content[71]. In most studies to date, collagen content is increased in muscle obtained from patients with cerebral palsy, as is the relative volume of the extracellular space compared to the cellular mass (FIG. 6e–h). Although increased collagen content and extracellular space volume correlate with increased stiffness, they do not correlate well with biomechanical tissue properties such as the Young modulus or stiffness measured in the same samples[71]. The structure of the ECM (collagen organization and crosslinking), as well as other non-collagenous constituents, such as hyaluronic acid, decorin, biglycan and uronic acid, may also influence biomechanical properties[70].

In addition to the changes in the ECM, increased stiffness of single fibres has been reported in the wrist flexors and calf muscles of individuals with cerebral palsy[66,72], but not in the hamstrings[67], compared with cells of the same muscle type obtained from age-matched typically developing children. The structural basis for these cellular changes is not known, although the giant intramuscular protein titin, which extends half the length of the sarcomere[73], does not seem to be involved[67].

Muscle transcriptional profiling. Transcriptome analysis of the muscle of children with cerebral palsy (of upper extremity wrist extensors and one of the hamstring muscles) points to several abnormalities[74,75]. For example, muscle from typically developing children does not express any of the developmental myosin heavy-chain isoforms (a type of myosin normally found in neonates or young children), but muscle of individuals with cerebral palsy does, suggesting that cerebral palsy is associated with a more immature type of myosin. Similarly, within the ECM, there is a paradoxical increase in both the matrix metalloproteinases (MMPs) and their inhibitors (tissue inhibitors of MMPs)[76], which may indicate a large increase in ECM turnover. Another dramatic change observed in cerebral palsy muscle transcription is the considerable increase in the expression of parvalbumin (a Ca^{2+}-buffering protein). Although parvalbumin regulation is poorly understood in mammalian muscle, this seems to indicate that the muscle is subjected to chronically increased Ca^{2+} loads.

Muscle stem cells. Another fundamental change in muscles affected by contracture, which may have direct therapeutic implications, is a decrease in the number

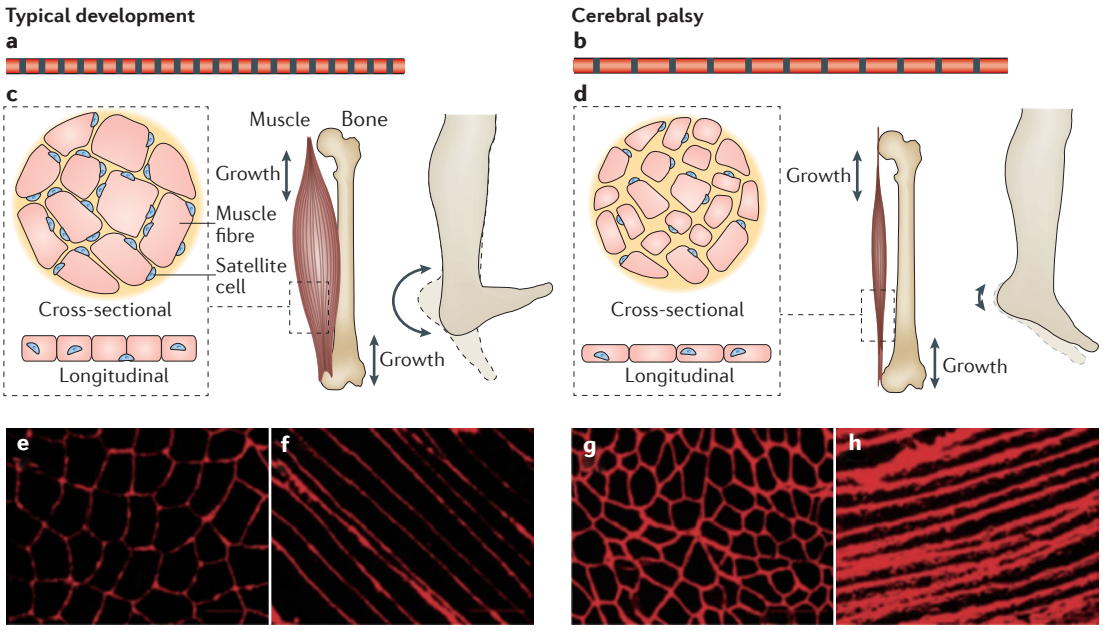

Figure 6 | **Structural changes observed in muscle of children with cerebral palsy compared with typically developing children. a**,**b** | Schematic representation of the long sarcomere lengths observed in children with cerebral palsy (part **b**) compared with the shorter sarcomere lengths observed in typically developing children (part **a**). This dramatic sarcomere length difference is observed even though the overall fascicle lengths of the two muscles are nearly identical[68]. **c**,**d** | Schematic representation of the growth in muscle from typically developing children as bone length increases. Sarcomeres are added in series as the bone grows, and therefore the ankle retains full range of motion (part **c**, right image). However, in a child with cerebral palsy, we hypothesize that sarcomeres are not added in series and thus, as the bone grows, the ankle is forced into plantar flexion (part **d**, right image). In the panels on the left, the microscopic appearance of muscle is shown. In cross-sections, muscle fibres from typically developing children are larger compared with fibres of children with cerebral palsy. In addition, in longitudinal sections, fibres from typically developing children have more satellite cells compared with children with cerebral palsy. **e**–**h** | Immunohistochemical staining of human muscle for laminin, one of the constituents of the extracellular matrix (ECM). Part **e** and part **g** are cross-sections, whereas part **f** and part **h** are longitudinal sections. Note the increased amount of ECM in muscle from children with cerebral palsy (part **g** and part **h**). Part **c** and part **d** adapted with permission from REF. 77, Wiley. Parts **e**–**h** reproduced with permission from REF. 67, Wiley.

of muscle stem cells — known as satellite cells. The muscle satellite cell is widely regarded as the precursor cell that is responsible for the majority of the growth in skeletal muscle[77] and is crucial for muscle regeneration[78]. Specifically, flow-assisted cell-sorting (FACS) methods have shown that the number of satellite cells is reduced by approximately 70% in muscles of children with contractures compared with age-matched typically developing controls[79]. However, FACS technologies may be vulnerable to the physical condition of the tissue; satellite cells of healthy muscle are more likely to be released by enzymatic digestion methods than cells from muscle of those with cerebral palsy owing to the excess ECM[79]. Independent studies that identify satellite cells based on a surface marker, co-localization with the nucleus and sub-sarcolemmal location were recently reported and supported the FACS finding, therefore, the results are not dependent on measurement method[77].

However, if the number of satellite cells is indeed reduced, it would suggest some type of developmental or maturation defect in muscles that develops in the context of cerebral palsy. Indeed, the decreased number of satellite cells could explain the reduction in fibre size, with impaired muscle growth as a consequence. Increased sarcomere length could result from a decreased ability of cerebral palsy muscle to add sarcomeres in series, which normally allows a healthy muscle fibre to grow in length while maintaining a near-constant sarcomere length[80] (FIG. 6c,d). Finally, the excess ECM observed in individuals with cerebral palsy may in part be caused by the decreased number of satellite cells[81], which has been shown to lead to excess muscle ECM in other experimental models[82] through the activation of the WNT signalling pathway.

The findings in this area seem to be converging on an understanding of the growth and regulation of satellite cells and tissue fibrosis[83]; given that this is an active area of research, the future bodes well for treatment of these devastating consequences of cerebral palsy. It is easy to envision therapies that involve small-molecule activation of satellite cells, inhibition of some or all of the WNT pathway, direct injection of myogenic precursors or even direct injection of appropriate genes in conjunction with or instead of orthopaedic surgery. Future studies are required to determine if and how CNS lesions alter muscle satellite cells.

Animal models

Various animal models (including rodents, primates, sheep, llamas and pigs) have been developed to investigate the mechanisms of brain lesions and the functional outcomes of particular brain lesions at a given time[84]. Animal models also enable investigators to test potential therapeutic approaches for cerebral palsy. However, the marked differences in motor and brain development between many animals and humans complicate comparison[85]. Rodents show postnatal brain development, with most myelin formation after birth, whereas in humans and most mammals, including non-human primates, the brain mainly develops *in utero*. Thus, the period from embryonic day 18 to postnatal day 7 is commonly used in rodents to model human early third-trimester lesions. Differences in motor systems also limit the relevance of animal data. For example, rodents differ markedly from humans in corticospinal tract projections, which are particularly crucial in cerebral palsy. Yet, some rodent models show interesting advantages, including mimicking human plasticity or study of adaptive motor control[86]. Valuable insights have been obtained from kittens with regard to the plasticity of the developing corticospinal pathways[87], despite some notable differences in corticospinal projections between cats and humans[88]. The main difficulty for addressing clinical features in most models is the lack of marked motor impairment resembling cerebral palsy in surviving animals. A promising exception has been documented in a rabbit model of fetal hypoxia[89]. Rabbits show perinatal brain development with myelination commencing soon after birth. In this model, increased limb muscle tone has been correlated with timing of insult.

Dystonia and spasticity

Spasticity is a clinical phenomenon in which muscles overreact to rapid stretch. By contrast, dystonia is defined as a movement disorder characterized by sustained or intermittent muscle contractions or co-contractions (that is, simultaneous activation of muscle groups across one or more joints) causing abnormal and repetitive movements and/or postures. Dystonia and spasticity have distinct pathophysiological features that require different management strategies. The physiological scheme of motor dysfunction is summarized in FIG. 7. Each component — that is, the movement, posture and stretch reflex disorders and the trophic changes in muscles — has distinct operational definitions set in a framework of electromyographic activity or inactivity, influenced by sleep and vestibular inputs. Many medical and surgical options for managing the movement disorders associated with cerebral palsy have been described[90,91]. Up to 17% of people with cerebral palsy have normal MRI brain scans, a figure that rises to 50% for those with dyskinetic cerebral palsy. Genetic and metabolic disorders, such as the dopa-responsive dystonias, aromatic L-amino acid decarboxylase (*AADC*) deficiency as well as glucose transporter (*GLUT1*; also known as *SLC2A1*) deficiency may mimic cerebral palsy owing to the early onset of movement disorders, including dystonic features and motor delay.

Dystonia. Dystonic movements are typically patterned or twisting and can be tremulous, interfering with voluntary movements. Dystonia is often initiated or worsened by voluntary action, the intention to move and non-specific stress, emotion or sensations[92]. Dystonia can be developmental, task dependent and pathological. In young children, the presence of tonic labyrinthine postures produce the typical picture of scissoring, which is exaggerated when lying supine, in vertical suspension and is reversed when held upside down, but is always abolished by sleep. In all cases of cerebral palsy, the influence of sleep, which transiently switches off dystonia and tonic labyrinthine postures, should be considered[93] (FIG. 7).

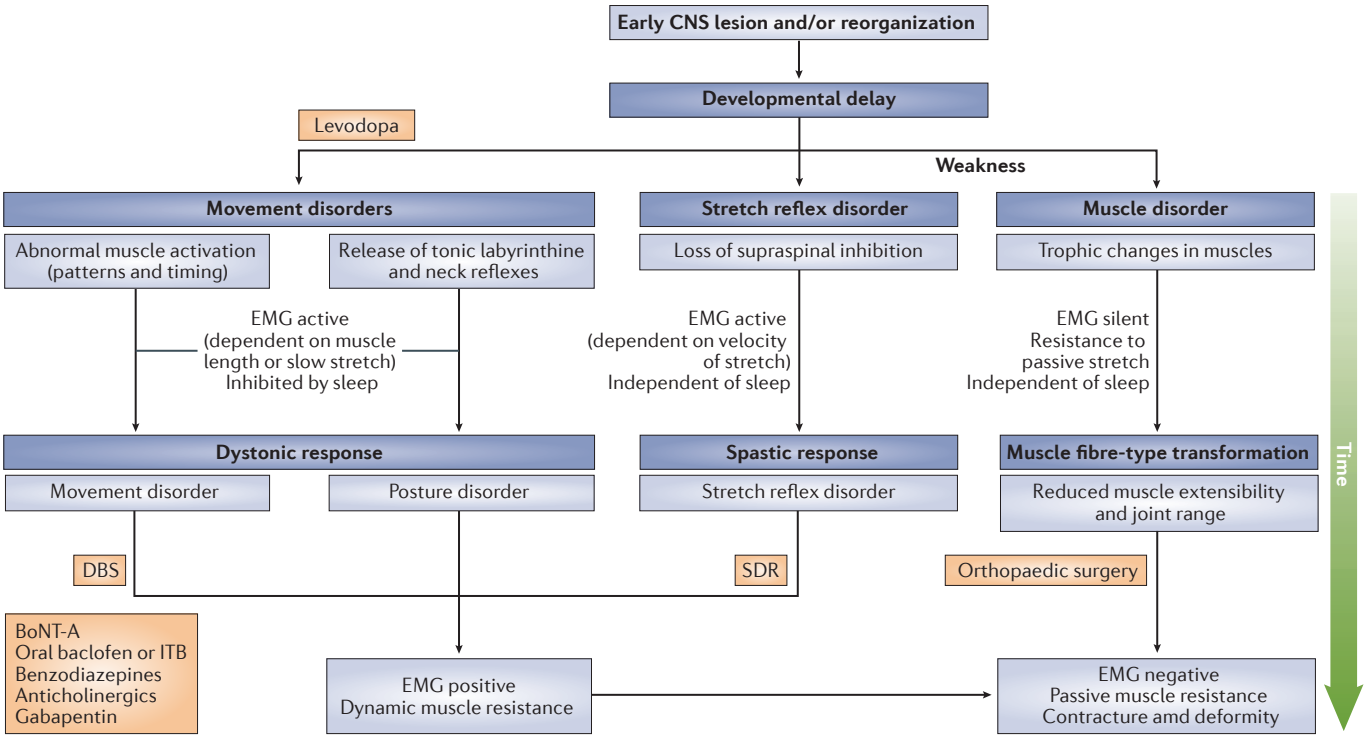

Figure 7 | **Movement disorders in cerebral palsy.** Central nervous system (CNS) lesions and/or reorganization can lead to movement disorders, which can be electromyographically (EMG) active or lead to EMG-silent trophic muscle changes and contracture. When the movement disorders are independent of sleep, loss of supraspinal (central) neuronal inhibition should be suspected, leading to a spastic response characterized by a disorder of velocity-dependent stretch reflexes. Dystonic disorders are inhibited by sleep and either present as a movement disorder (abnormal proximal-to-distal muscle sequencing with co-contraction) and/or a postural disorder (abnormal tonic labyrinthine reflexes, with scissoring or fisting). In dystonia, sustained EMG discharges are present 'at rest' and are length dependent (worsened by slow stretch) and arousal dependent. The majority of management strategies that have emerged over the past 70 years are depicted in the orange boxes. Management depends on the patient characteristics. All management plans aim to support innate adaptive motor development, but the anatomy and physiology of the muscles in cerebral palsy inexorably tends towards fixed, irreversible deformity and muscle contracture over time. Management strategies include seating systems, communication aids, neurosurgical interventions (deep brain stimulation (DBS), intrathecal baclofen (ITB) and selective dorsal rhizotomy (SDR)), pharmacological approaches and orthopaedic surgery: all within a multidisciplinary team and according to the WHO International Classification of Function Children and Youth version 2007 (WHO-ICF-C-Y 2007)[91]. BoNT-A, botulinum neurotoxin A.

Characteristic features of dystonia include[94]: co-contraction and overflow muscle activation (excessive recruitment of muscle groups that are not directly required for a task); difficulty switching between component movements of complex tasks; and reduced spinal cord and brainstem inhibition. However, co-contraction can be a normal physiological process. For example, during development, the fetus assumes opposing flexor and extensor postural stages[95] characterized by co-contraction; these co-contractions precede and accompany the development of voluntary movements. This process can be arrested or prolonged in cerebral palsy, depending on the site, timing and severity of the brain injury or reorganization.

Newborn mammals exhibit polysynaptic muscle innervation. Reciprocal inhibition of opposing muscles leads to gradual suppression of the reciprocal stretch reflexes, owing to an activity-dependent elimination of redundant synapses in these muscles a few weeks later[96]. However, this process can be disturbed in cerebral palsy and replaced by persistent reciprocal reflex excitation and reduced reflex inhibition[97]. Polysynaptic or exuberant over-innervation can persist if activity is impaired, especially when limbs or joints are immobilized following tenotomy (that is, surgical division of a tendon) or after chronic local anaesthetic blockage of nerve impulses[98]. A similar phenomenon can occur in preterm babies and sick neonates, who move less and may undergo neuromuscular paralysis for ventilation, or as a consequence of cerebral brain injuries, leading to cerebral palsy.

Young children have little limb inertia and stiffness; muscle twitches are weak and slow; and developmental co-contraction results in coarse motor performance[99]. Co-contraction is, therefore, the norm in the first few years but (alongside joint synchronies) offers postural stability at the expense of mobility. Sutherland *et al.*[100] found prolonged calf-muscle activation during walking in two-thirds of typically developing 1-year-old children and one-third of 7-year-old children, producing an equinus gait (toe walking), in which the foot

points downwards (plantar flexion) in terminal swing. Co-contraction diminishes as movements become more graceful and functional in unsupported walking in typically developing children, but persists during walking in children with cerebral palsy[101].

Children and adolescents can exhibit task-dependent overflow or dystonia. Indeed, all 4-year-old children and 25% of 16-year-old children exhibit involuntary postures of the face, tongue, arms or hands during unfamiliar tasks[102]. Task-dependent dystonia can persist with learning difficulties and motor impairments[102]. Increasing speed of walking also leads to more task-dependent co-contraction[103]. All infants and many children with cerebral palsy have a crouch gait that is very tiring to sustain and is accompanied by rushing forward, dashing or hurrying, also leading to task-dependent co-contraction. Fluency and mobility are sacrificed for stability.

Children with cerebral palsy have poor motor selection resulting in excessive motor activity[104]. Typically developing children and healthy elderly individuals recruit larger areas of the cerebral cortex than young adults[105]. A lack of selective motor control, excessive synaptic plasticity and loss of surround inhibition are also hallmarks of dystonia, leading to too many simultaneous muscle activation patterns during a task rather than those most appropriate for the task[106,107]. This may be why dystonias occur in the young and elderly when motor patterns are less focused and in cerebral palsy when normal motor development fails. Movements are normally modulated by sensory, motor, cognitive and limbic subdivisions of the basal ganglia and their projections to the thalamus and from there to the respective cerebral cortex[108], forming parallel but necessary interacting loops of function linking drive, motor planning, execution and feedback, also modulated by the substantia nigra and the cerebellum. Children with cerebral palsy respond poorly to unexpected perturbations. When suddenly tilted forwards or backwards, typically developing children stabilize the ankle followed by the knee joint producing a 'distal-to-proximal' muscle activation[109]. In children with hemiplegia or diplegia, a 'proximal-to-distal' activation sequence occurs when tilted forwards or backwards, which is an abnormal pattern that is not found in typically developing children or in children with ataxia and in the uninvolved leg of children with hemiplegia[109]. Inputs from the vestibular (balance) system facilitate functional postures, altered according to head position. Such tonic labyrinthine reflex postures are exaggerated in many children with cerebral palsy when they are observed lying in supine, vertical suspension or upside-down positions. These abnormal muscle activation sequences and the tonic labyrinthine reflexes give rise to muscle co-contractions, are abolished by sleep, are different to spasticity and could be the target of future specific interventions in children with cerebral palsy.

Dystonia may have a severe effect on children. In one study involving 279 children who were referred to a centre specializing in deep brain stimulation, at the time of referral 60% showed worsening of their dystonia, dystonia remained severe in 30% and was improving in fewer than 8%[110]. The causes of dystonia in this study were cerebral palsy (in 54%), acquired brain injury (in 18%), heredodegenerative disorders (in 10%), primary dystonia (in 11%) and dystonia-plus syndromes (in 7%)[110]. In a review of 70 interventional studies of dystonia, the aspects that mattered most to children (pain, activities of daily living, manual function and sitting) were not measured[111] (FIG. 7).

Spasticity. The currently accepted physiological definition of spasticity was framed by James Lance[112] and highlights the importance of the velocity-dependent stretch reflex. Indeed, the stretch reflex response increases approximately linearly with the increase in the velocity of stretch. The reflex component of the increased tone might, therefore, be measured in terms of the threshold velocity required to evoke reflex activity and the slope of the electromyography–velocity relationship.

Spasticity only partially explains poor gross motor function (floor skills, standing and walking) in those with cerebral palsy[113]. Important positive relationships were found between strength, gross motor function and functional outcomes, indicating that weakness accounts for more disability than spasticity[113]. This prompted a call for activity-based rather than impairment-based interventions[113]. Velocity-dependent stretch reflexes can be reduced by oral baclofen (a γ-aminobutyric acid agonist used as a centrally acting muscle relaxant) and by biofeedback methods, but such spasticity reduction does not necessarily improve functional gains[114]. Co-contraction in dystonia of the quadriceps and hamstring muscles may not be suppressed with small doses of oral baclofen, despite a reduction in the velocity-dependent stretch reflexes[114]. Spasticity is not the cause of the typical equinus posture (toe walking) typically seen in children with cerebral palsy[115]. Elegant pharmacological studies on baclofen receptor distribution in the Rexed layers of the spinal cord[116] explain why dorsal rhizotomy cannot alter postures but baclofen may, indicating that dorsal rhizotomy should not be considered as a cheaper alternative to intrathecal baclofen. However, baclofen can also induce floppiness, postural relaxation, drooling, drowsiness and, in high doses, may provoke coma and respiratory depression that can be life-threatening.

Stretch reflexes in individuals with cerebral palsy change over time and after interventions[117]. Exercise, immobilization, surgery or disuse alter the stretch reflex excitability, clonus (rhythmic muscle twitches)[117] and the visco-elastic properties of muscle[118,119] even though the cerebral lesion remains unchanged[117]. In a review of 15 studies in children with cerebral palsy[120], spasticity remained poorly defined and measured. The development of methods to distinguish neural from non-neural resistance to muscle stretch continues (FIG. 7).

Dystonia may coexist with chorea (jerky, dance-like movements) and athetosis (slow, writhing movements) often referred to collectively as dyskinetic (dystonic–choreoathetoid) cerebral palsy, which accounts for 6–14% of all cerebral palsy[42,121]. MRI brain scans can be normal in 11–17% of children with cerebral palsy[122].

Intact corticospinal tracts but wasted posterior thalamic radiations may be found in periventricular leukomalacia, which is a type of white matter brain injury commonly found in individuals with cerebral palsy[123]. Central motor conduction times in children with cerebral palsy, including periventricular leukomalacia, may be normal[124,125]. Dyskinetic cerebral palsy may occur with normal neuroimaging in 50% of children[122]; the remaining cases having periventricular leukomalacia and basal ganglia, thalamic and cerebellar abnormalities. Findings of periventricular leukomalacia do not automatically equate with spasticity and, therefore, dyskinetic cerebral palsy is probably underestimated[91,126].

Cerebral palsy produces delayed and abnormal motor development and may cause retained immature motor strategies, including developmental co-contraction and poor selective control of movements. Dystonia and spasticity, usually separately but sometimes in combination, are components of the movement disorder of cerebral palsy. New targeted interventions, such as deep brain stimulation, and older denervation techniques, such as selective dorsal rhizotomy, pharmacological interventions (for example, gabapentin, which seems to be better tolerated for dystonia)[127] and strengthening management strategies, demonstrate why greater understanding of this complex movement disorder is required to improve functional outcomes in children with cerebral palsy. The motor severity of cerebral palsy — including the dystonic–dyskinetic forms — may be accurately evaluated and compared with genetic and heredodegenerative dystonias using the same scales commonly used within the cerebral palsy literature[128]. Dystonia has a severe, lifelong impact in children with cerebral palsy[110] and more successful management strategies are urgently required.

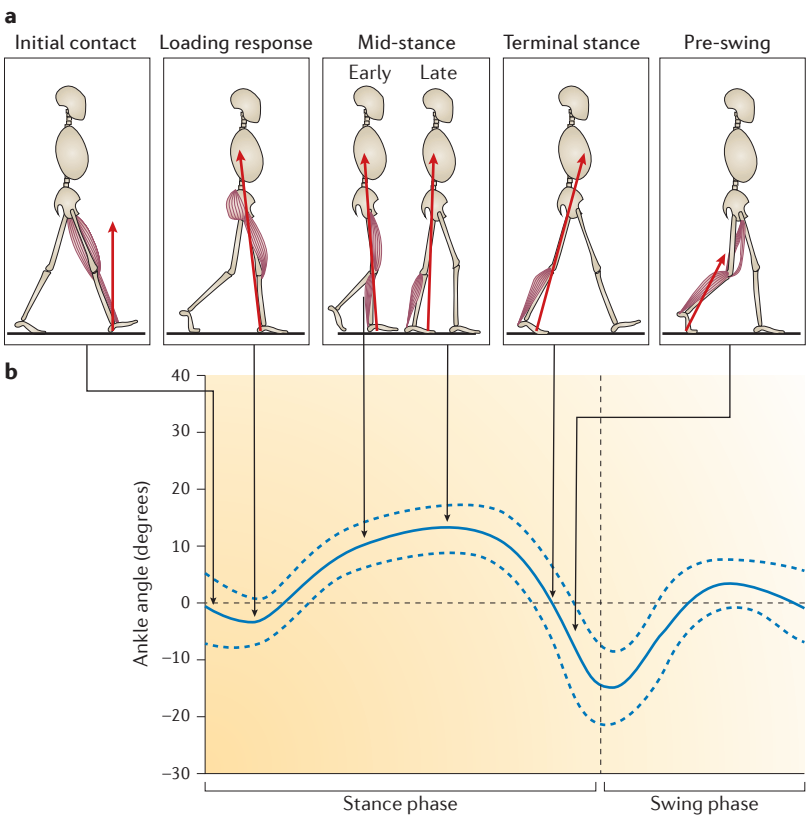

Figure 8 | **Stance phase and sagittal ankle kinematics: typically developing gait.** **a** | Stance phase can be divided into sub-phases that may include: initial contact, loading response, mid-stance, terminal stance and pre-swing. In each of the phases, the direction of the ground reaction force is indicated by the red arrow. **b** | The angle of the ankle is indicated, with the solid blue line indicating mean ankle dorsiflexion for typically developing gait and the dashed blue lines indicating two standard deviations around the mean.

Diagnosis, screening and prevention

Diagnosis

Motor dysfunction and brain lesions. Cerebral palsy is the result of a non-progressive lesion or injury to the developing brain and has multiple causes and clinical manifestations, thus making a discussion on diagnosis and screening challenging. In the past, the diagnosis of cerebral palsy was largely a clinical diagnosis, principally based on the recognition of features, such as a delay in reaching motor milestones and changes in muscle tone or reflexes. With the development of imaging, including both cranial ultrasonography and brain MRI, the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society has recommended that, where possible, the clinical diagnosis of cerebral palsy should be confirmed by imaging[129]. A further development in clinical assessment is the renewed interest in the qualitative assessment of general movements. This diagnostic tool consists of observing the infant for a period of between 5 minutes and 20 minutes and assigning a qualitative rating of the quality of the infant's spontaneous movements[130,131].

Gait analysis. Since the 1970s, clinical gait analysis has been used in the assessment of children with cerebral palsy[132]. Gait analysis was mainly used for research purposes, but progressively it has been more widely used to support clinical decision making and in outcome studies. The development of camera and computer technology has supported the wider availability of gait analysis systems.

There are several technical systems for clinical gait analysis available to measure joint kinematics: biplanar video observation, 3D passive-marker systems with infra-red cameras, 3D active-marker systems with light-emitting diodes and, recently, with inertial sensors. Ground reaction forces can also be measured and joint kinetic data computed. The data captured by the system are imported into biomechanical models, with output in graphical format in the sagittal, coronal and transverse planes (FIG. 8). There are free walkway systems and systems integrated into treadmills, with or without virtual reality environments. Surface and fine-wire electromyography can also be captured, providing crucial information regarding the activation of muscle groups during walking[132].

Using this technology, pathological gait in cerebral palsy can be classified using both clinical and biomechanical classification systems. Hyperactivity of the soleus muscle in loading response and mid-stance may

cause hyperextension of the knee, with decreased forward progression of the tibia. Weakness of the soleus muscle in loading response may cause increased knee flexion and increased forward progression of the tibia. Hyperactivity of the gastrocsoleus muscle in mid-stance may cause knee extension (or hyperextension) with heel rise. Weakness of the soleus muscle with hyperactivity of the gastrocnemius muscle may cause knee flexion with heel rise. In terminal stance and/or pre-swing, hyperactivity of the gastrocnemius muscle may block full knee extension, but insufficient propulsion may also result in excessive knee flexion. Several gait classifications have been described, and although these have some clinical use, they represent a substantial simplification of complex biomechanical data[133] (FIG. 8).

The effects of a stiff as opposed to a shortened or hyperactive muscle are biomechanically equivalent; only by physical examination can these conditions be distinguished.

Screening

Any infant who has known risk factors — including *in utero*, antenatal or birth-related factors — should be considered at risk and enhanced screening should be offered. The strongest of these risk factors include prematurity and hypoxia–ischaemia. A combination of assessment of general movements with cranial ultrasonography and, when available and appropriate, MRI scanning, will enable the diagnosis of cerebral palsy with a very high level of sensitivity and specificity[134].

Two additional points are worth making. First, approximately 11–17% of children with a diagnosis of cerebral palsy on clinical grounds will have normal MRI scans[135]. These children in particular should be investigated carefully to exclude genetic and metabolic conditions. Second, given that many children with cerebral palsy have no known risk factors, all infants and children should still be screened for abnormalities of motor development, for example, delays in sitting, standing or walking, early hand preference, asymmetric patterns of crawling or walking, or abnormalities of muscle tone. Regular checks by both child health care nurses and family doctors are essential, with referral to paediatricians, paediatric neurologists and early childhood intervention services of children when there is concern.

Prevention

Some specific cerebral palsy subtypes have clear risk factors (for example, rhesus isoimmunization, maternal iodine deficiency, thyroid disease or hyperbilirubinaemia), and prevention strategies have been developed that have been successful, particularly in middle-income and high-income countries. However, when cerebral palsy results from the interaction of multiple factors along a causal pathway, prevention is infinitely more challenging. For example, a mother who conceals her pregnancy, smokes and takes recreational drugs in combination with a poor diet and delivers a premature infant outside of the hospital, may have multiple contributing factors to the potential brain injury in the premature infant. In such circumstances, secondary prevention may be more effective than primary prevention. Secondary preventive strategies may include efforts to reduce prematurity, for example, cervical suture to prevent premature birth in mothers with cervical incompetence[136] and tocolytic medications to delay the onset of labour[137,138]. Magnesium sulfate has been shown to be effective in reducing the risk of cerebral palsy when administered to women at risk of preterm birth[25], as have antenatal steroids when administered before 34 weeks of gestation[139]. Whole-body cooling has been shown to be effective in reducing the risk of death and severity of neurodisability when commenced within 6 hours of birth[32].

Management

Disordered control of muscles and movement in people with cerebral palsy can be associated with a wide range of functional challenges. Traditional efforts to manage these motor disabilities have been directed at 'normalizing' tone and promoting 'normal' motor patterns. Conversely, contemporary approaches to treatment are addressing muscle weakness as a common element of functional challenges with encouraging results.

Physiotherapy

Given that the hallmark of cerebral palsy is a motor disability, physiotherapy has long been central to the clinical management of children with these disorders. Children are often referred to physiotherapy as soon as the diagnosis is confirmed or suspected. Therapy may offer many benefits to patients and their families, such as a detailed assessment of motor capabilities to identify strengths as well as possible targets for intervention, provision of mobility or positioning aids to improve daily functioning, and as a source of support and cerebral palsy-related health information. The most extensively investigated aspect of therapy is direct intervention, such as upper or lower limb motor skill training facilitated by the therapist. This has slowly transformed over the decades from approaches based mainly on clinical observations or assumptions, such as the longstanding speculation that spasticity was the primary cause of the motor difficulties to paradigms supported by emerging biomechanical, neurophysiological or motor learning principles as summarized in REF. 140. Even though accumulating evidence has failed to support more-traditional approaches, such as Bobath or Vojta therapy[141], these and other approaches are still remarkably prominent, especially in developing countries and among stalwart practitioners. However, rapid progress in neuroscience and other fields such as exercise science and genetics have and will continue to inform advances in therapy approaches for those with motor disabilities as a result of cerebral palsy.

A primary goal of physiotherapy intervention is to enhance a functional motor activity that is prioritized by the child and the family. The two main types of intervention that have been shown to be effective in individuals with cerebral palsy are task-specific skill training to improve motor coordination and performance (that is, constraint-induced movement therapy, a form of

therapy that combines restraint of the unaffected limb to encourage intensive use of the affected limb), and physical training to address an underlying, perhaps secondary, impairment (for example, weakness or decreased fitness) that may be limiting performance of the desired activity. General principles have emerged to differentiate effective neurorehabilitative therapies[142]. To maximize motor learning, the patient must be actively engaged in the task both physically and mentally, the regimen must be sufficiently intense and practice, although task specific, should also be variable and incrementally challenging. Less-successful approaches include passive handling or manipulation of the subject via the therapist's hands or an external device such as an exoskeleton or rote practice (memorizing a technique based on repetition) such that both the patient and the nervous system disengage or habituate to it.

Evidence clearly supports the use of activity-based approaches in physiotherapy[140,141]. The most consistently and well-supported therapy intervention in cerebral palsy is intense upper limb training for improving hand function in children with unilateral involvement[141,143]. Training types and formats vary across studies, with fairly uniform success rates given sufficiently intense and frequent regimens. Task-specific protocols in the lower extremities have not demonstrated similarly strong and consistent effects. Possible explanations are that regimens are typically not as great in lower limb trials compared with upper limb trials, devices may assist too much, or the training may not be sufficiently salient or motivating to the participant[144]. Virtual reality paradigms could intersect with training regimens to optimize engagement and augment learning[145]. Reports citing the lack of superiority of weight-supported treadmill training or robotic-assisted training over equally intense motor training alone are both surprising (based on early evidence supporting their effectiveness) and discouraging. However, the rationale is clear for using devices — from functional electrical stimulation electrodes to lower limb exoskeletons — to enable those with limited movement repertoire to perform and practice movements that are difficult or impossible for them. More efforts should focus on the design of devices that optimally challenge the motor system and are more-precisely tailored to individual capabilities. Harnessing the experience-dependent plasticity of the nervous system that enables one to improve motor skill with the appropriate type and amount of practice has led to successful upper limb outcomes, but has not yet been fully exploited in lower limb training protocols.

People with cerebral palsy may reduce the amount and types of activity during adolescence and early-to-mid-adulthood, which can exacerbate disability owing to the progressive development of secondary impairments that, in turn, make it even more difficult to move. Regular physical activity can prevent or reverse this decline and help to maintain function as well as reduce associated adverse health outcomes from inactive lifestyles[146]. Even the most functional children with cerebral palsy are substantially weaker and have poorer aerobic fitness than their peers without cerebral palsy[147,148]; the level of weakness and aerobic fitness varies by the Gross Motor Function Classification System (GMFCS) level. The subjective report of fatigue in individuals with cerebral palsy is also directly related to the degree of weakness[149], forcing those with cerebral palsy to operate close to their maximal capacity even when performing normal daily activities such as walking.

Although a recent review of lower extremity therapy techniques cited strengthening as the most effective option for improving gait and gross motor function[150], the literature on strengthening in cerebral palsy is inconsistent. Recent recommendations are that the approach to strengthening in cerebral palsy may need to be more targeted to the individual muscles whose weakness is most limiting to the motor task performance[151] owing to the abnormal muscle imbalances that, if not addressed, can lead to musculoskeletal issues, such as contracture and bony deformities. Functional or whole-leg-strengthening programmes[152,153] have been notably unsuccessful, probably because the stronger muscles dominate over those key weaker muscles during training tasks and become even stronger and/or tighter. Where possible, strengthening weaker muscles at a joint through targeted resistance training and/or functional electrical stimulation is preferable over strategies that aim to correct imbalance by blocking or weakening the stronger muscle (for example, orthoses (external braces that cross the joint and thereby limit joint motion), botulinum neurotoxin A (BoNT-A) injections or muscle–tendon lengthening). The short-term activity programmes have limited benefit in cerebral palsy[154], which is perhaps not surprising given that physical training benefits accumulate over time and may need to be evaluated over a protracted period when functional changes become evident.

Strength and fitness programmes should not be considered as therapy interventions but rather as crucial components of a healthy lifestyle for everyone, something that is even more important for those at higher risk of inactivity. The role of the therapist is mainly to help their patients with cerebral palsy identify effective sustainable strategies for incorporating intense physical activity in their lives and, perhaps, training specific capabilities that will increase their exercise capacity. Aquatic activities are particularly beneficial for people with severe and less-severe cerebral palsy, given sufficient training and supervision. New exercise devices are being developed that provide various types of assistance for those with physical challenges.

Musculoskeletal pathology management

As children with cerebral palsy grow, the effects of the brain lesion extend to most parts of the musculoskeletal system[155]. The interaction of the positive and negative features of the upper motor neuron lesion are responsible for the specific musculoskeletal pathology in cerebral palsy subtypes and the specific anatomical locations[156,157] (FIG. 9). Biomechanical and biological pathways to musculoskeletal deformities include inhibition of longitudinal growth in muscle–tendon units and long bones, muscle imbalance and hypertonia, altered

gait biomechanics and weakness resulting in reduced activity[158,159]. Reducing hypertonia using oral medications, injections of BoNT-A and intrathecal baclofen have minimal effects on the progression of fixed muscle contractures, even when combined with optimal physical therapy. Surgery for fixed contractures and skeletal malformations can be delayed but not prevented.

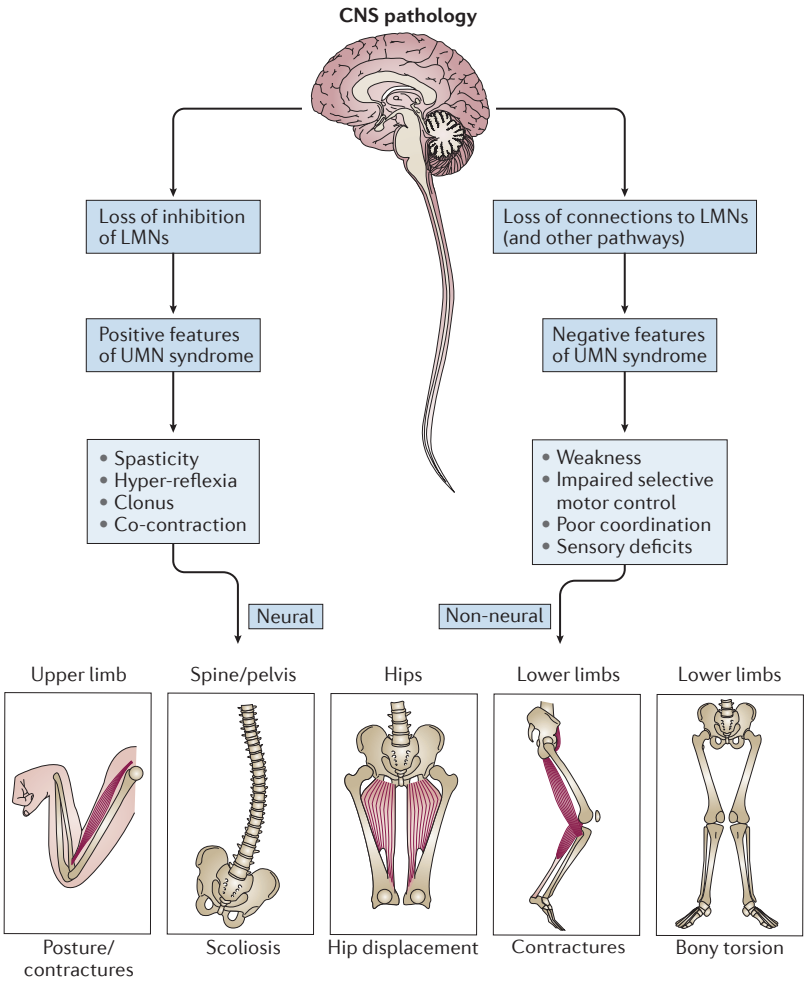

Figure 9 | **Upper motor neuron syndrome.** In cerebral palsy, the injury to the upper motor neurons (UMNs) results in two kinds of effects. The predominant and most important effect results from loss of corticospinal tract connections to lower motor neurons (LMNs) and hence to skeletal muscles. This causes paresis or partial paralysis, which is usually more pronounced for distal muscles than proximal muscles. By contrast, hypertonia is hypothesized to be caused by the loss of inhibitory descending input to the LMNs, which keeps the stretch reflex in the peripheral neuromuscular system from being overactive. This results in hypertonia and hyper-reflexia. The effects of the brain lesion in children with cerebral palsy may extend to all parts of the musculoskeletal system, particularly in children with more-severe motor impairment. Some of the typical postures and deformities in the upper limbs, the spine and pelvis, the hips and the lower limbs (contractures and long bone torsion) are shown. In general, the effects of the UMN syndrome can be considered as a group of 'positive' features (for example, too much tone) and as a group of 'negative' features (including too little selective motor control and strength). Traditionally, the positive features and their amelioration by intervention strategies have been overemphasized. By contrast, the negative features have received much less attention until recently. For example, hip displacement has largely been attributed to adductor spasticity and contracture, but management based on alleviating these features has little effect. Recent studies that report a linear relationship between the prevalence of hip displacement and Gross Motor Function Classification System level strongly suggest that it is the negative features that are more important. CNS, central nervous system.

Contractures. Cerebral palsy has historically been called 'short muscle disease' owing to the prevalence of contractures[158,160]. Shortening is at first 'dynamic' — secondary to hypertonia. Normal length is present under anaesthesia, and management is focused on non-surgical interventions. With time, fixed contractures develop. These are still present under anaesthesia and surgical lengthening may be required.

Muscle–tendon units in children with cerebral palsy rarely shorten, they simply fail to lengthen enough to keep up with the growth of the neighbouring long bone[158]. With time and with the growth of the long bones, progressive contractures develop. In the Swedish longitudinal study of a population of children with cerebral palsy, spasticity increased until 4 years of age and then decreased each year until 12 years of age[161]. As children with cerebral palsy grow, the Swedish programme reported a steady decrease in the range of motion of joints from 2 years of age until 14 years of age as fixed contractures develop[162].

Muscles that cross two joints are more prone to contractures than muscles that cross a single joint. This observation forms the basis for standard physical examination techniques, for example, measuring the range of ankle dorsiflexion with the knee flexed and then extended[160,163]. Some surgical procedures are designed to recess or transfer two-joint muscles to make them function as one-joint muscles[164–167].

Spastic contractures are reversible under conditions of relaxation and include postures such as equinus. These contractures may respond to non-operative management, including casting and splinting, or intramuscular injections of BoNT-A in younger children[168]. However, injections of BoNT-A result in reduced muscle torque (the tendency of a force to rotate an object), weakness and atrophy of skeletal muscle[169,170] and atrophy of the underlying bone[171]. More information is required from both animal studies and long-term clinical studies to fully assess the benefits and risks of BoNT-A therapy[172].

Fixed contractures are managed by lengthening of the muscle–tendon unit by the technique that delivers the safest and most effective 'surgical dose' (that is, the surgical technique that gives the appropriate amount of lengthening of the muscle for the child in question)[165,173]. Many surgical techniques are available and different clinical outcomes can be expected in terms of both overcorrection and undercorrection. Precise lengthening of the contracted muscle–tendon unit has been shown to achieve correction of deformity and to improve gait and functioning in both the short term and the long term[173,174]. Surgical techniques should be tailored to the cerebral palsy subtype, and long-term follow-up studies with gait analysis, measures of activity, participation and health-related quality of life (QOL) are required to determine outcomes[175,176]. Orthopaedic surgery for contractures is rarely required before 6 years of age and outcomes are more predictable after this age. Strategies to try to prevent fixed deformities including positioning (that is, sleep systems, night braces and various forms of orthotic devices), casting and splinting are widely practised. Outcome studies are difficult to design and the evidence base is poor.

Torsion in long bones. The second major component of musculoskeletal pathology in people with cerebral palsy is torsion of long bones[155,158,160,177]. In a large population-based study, mean femoral neck anteversion was 40° (with normal being 15–20°) at GMFCS level III–V[178]. Abnormal torsion in the femora of children with cerebral palsy is not acquired because of spasticity but represents failure to remodel fetal anteversion[178–180]. Abnormal tibial torsion is also common[181–183]. Some children with cerebral palsy retain infantile medial tibial torsion, but the majority acquire external tibial torsion with growth and development as a response to abnormal biomechanical forces during walking[182,183].

Clinical measurement of femoral and tibial torsion is not reliable[160,184,185]. Improved accuracy and reliability are possible with axial imaging including CT and MRI[186]. These modalities are not ideal in children because CT involves large doses of ionizing radiation and MRI often requires general anaesthesia to acquire high-quality images[160,186]. Alternatives that can improve research in long bone torsion include 3D ultrasonography[187] and electro-optical system (EOS)[188,189].

Pathological torsion in ambulant children with cerebral palsy is managed by rotational osteotomy to fix the bone in a new, appropriate position, usually in the context of single-event, multi-level surgery[155]. This type of surgery encompasses the correction of all fixed contractures and torsional deformities of the long bones in the lower limbs, during one operative session, with only one period of rehabilitation as a consequence. This procedure resulted in large improvements in gait, small improvements in gross motor function and gains in all domains of the International Classification of Functioning in two cohort studies[190,191] and in the one randomized controlled clinical trial published to date[173]. Although this type of surgery is ideally performed between 6 years and 12 years of age, it can also have a role in carefully selected adults, although rehabilitation could be protracted and uncertain.

Hip displacement and spine deformity. Overall, hip displacement affects one-third of children with cerebral palsy, but is as high as 90% of children with severe cerebral palsy (GMFCS level V)[192]. The prevalence and risk factors for hip displacement have been established in large population-based studies in Australia and Sweden[192,193]. The risk of hip displacement, defined as a migration percentage of >30% (normal is <10%), was found to be linearly related to GMFCS level, but did not have a relationship to the type of movement disorder[192,193]. It seems that the negative aspects of the upper motor neuron lesion, but not the positive factors, are the causative factors in hip displacement[156,157]. The relationship between neuromuscular scoliosis (abnormal curvature of the spine) and GMFCS level is similar, with severe curves only evident in non-ambulant children in GMFCS level IV and GMFCS level V[194]. These findings have direct bearing on the understanding of the pathophysiology and management. Traditionally, great emphasis has been placed on adductor spasticity and adductor contractures 'pulling' hips out of joints by greatly increased forces[195]. However, children with hypotonia at a given GMFCS level have the same risk of hip displacement as children with hypertonia[192]. This suggests that it is impaired function — specifically phasic contracture of the hip abductors during walking — that is essential to normal hip development and stability[192]. This hypothesis explains the high failure rate following BoNT-A therapy[196] and adductor release surgery[197] for hip displacement in non-ambulant children with cerebral palsy. It also explains the high success rate of bony reconstructive surgery[198,199]. Optimal management of hip displacement in cerebral palsy requires population-based hip surveillance to determine the optimal timing for prevention and management, and appropriately timed preventive and reconstructive surgery[200,201]. Painful hip dislocation is preventable and salvage surgery can be avoided[193,198,201]. Evaluation of hip and spine interventions requires meaningful assessments in domains of most concern to individuals with cerebral palsy, parents and carers[202,203].

The effects of early postural management of scoliosis and seating systems require more long-term, controlled studies[204]. Bracing is not well tolerated and BoNT-A injections have adverse effects and are not effective[205,206]. Current evidence supports surgical management of scoliosis by a long instrumented fusion from T2 to the pelvis[207].

Both scoliosis and hip displacement may progress in young adults with cerebral palsy and management can be challenging. Total hip arthroplasty (a surgical procedure to restore the integrity and function of a joint by replacing the articular surface) gives reliable pain relief in carefully selected young adults with degenerative arthritis[208]. Large population-based studies and prospective cohort studies with long-term clinical and radiological follow-up monitoring offer the best opportunity for the study of the prevalence, mechanisms and management of musculoskeletal pathology in individuals with cerebral palsy[162,190,193,199].

Rehabilitation technology

Rehabilitation can provide a wide variety of opportunities to enhance the functional status of people with cerebral palsy. These interventions aim to promote people's abilities, even if what they do and how they achieve their goals are different from typical function. Rehabilitation technology includes assisting devices, which enhances participation in the community, as well as enhanced therapeutic options or extenders for physiotherapy.

Treatment with ankle foot orthoses related to gait. Pathological gait in the sagittal plane can be improved by the use of ankle foot orthoses (AFOs) (FIG. 10). For example, hyperextension of the knee in loading response or mid-stance can be corrected by various types of AFOs, including a dorsal shell AFO or a posterior leaf spring AFO. Excessive knee flexion can be partially controlled by alternative AFO designs, including an anterior shell AFO or a floor reaction AFO. Limiting dorsiflexion of the ankle to approximately 0° by blocking third rocker with a rigid ankle and footplate, will increase the knee

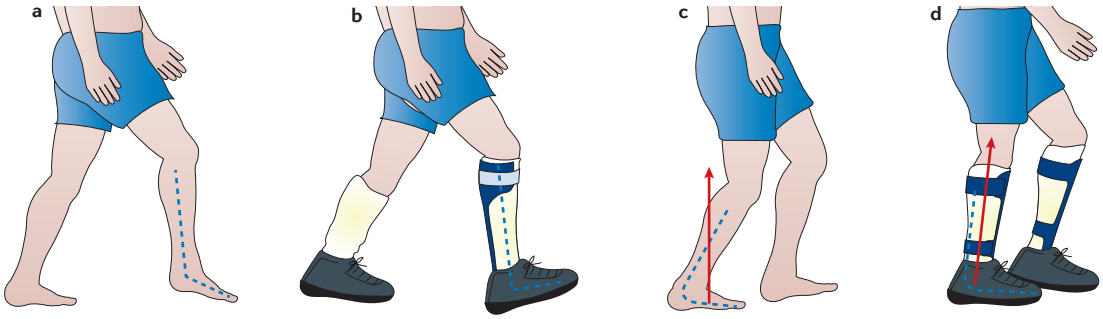

Figure 10 | **The role of ankle foot orthoses in ambulant children with cerebral palsy. a**,**b** | Ankle foot orthoses (AFOs) may be prescribed to improve gait and function for both swing-phase and stance-phase problems during gait. Part **a** and part **b** are based on sagittal plane videos of an 8-year-old boy with right spastic hemiplegia who attended the Hugh Williamson Gait Laboratory, The Royal Children's Hospital, Melbourne, Victoria, Australia. The right leg is in late swing and shows equinus (dashed blue line), which was the result of spasticity in the gastrocsoleus muscle combined with poor selective motor control. This leads to tripping and falling (part **a**). The AFO corrects the equinus, resulting in a normal heel strike and a more normal sequence of ankle rockers (part **b**). **c**,**d** | In older children and many adolescents with cerebral palsy, excessive knee flexion and crouch gait are common. In these figures derived from sagittal plane videos of a 12-year-old boy with spastic diplegia and crouch gait, neither the knees nor the hips extend fully in late stance. The red arrow indicates the direction of the ground reaction force, which is posterior to the knee. This results in an excessive demand on the quadriceps to prevent further sinking and falling. The ankle is also excessively dorsiflexed (part **c**). When bilateral floor reaction AFOs are worn, the ground reaction force is redirected in front of the knee, excessive ankle dorsiflexion is blocked and both the knee and the hip show improved extension, reducing the demand on the quadriceps and resulting in a more erect, energy-efficient gait pattern (part **d**).

extension moment at the time that hip extension and knee extension are possible. The majority of AFO designs are also able to prevent excessive plantar flexion of the foot during the swing phase of gait[209]. Deformities resulting in deviation in the coronal plane of the foot and knee (valgus, varus, inversion or eversion deformity) can be modified by AFOs, whereas rotational deviations are not influenced by AFOs. The range of motion can be influenced by the use of ankle joints in the AFO and some 'spring' effect added[210].

Rehabilitation technology to improve functioning and training. Technology has opened worlds for many disabled people, including people with cerebral palsy, through augmentation (for example, wheelchairs driven by finger movements) and substitution (for example, speech technology) technologies. Although mobility is the usual focus for parents of children with cerebral palsy in early childhood, language and communication are key in developing relationships and employment for adults with cerebral palsy. Access technologies or those devices that capture intent have advanced from simple mechanical switches to machine vision (that is, eye-gaze trackers), inertial navigational systems (that is, navigational aids that use motion and rotation sensors to calculate the position of a moving object) and emerging physiological interfaces that require minimal physical effort. Output devices for communication have evolved from bulky, dedicated hardware with limited configurability, to systems that run and function with many different platforms with highly personalized mobile applications[211]. The trend to provide mobility aids and augmentative communication options at earlier ages and earlier stages of cognitive ability[211–213] leads to positive social outcomes for the patient and parents[213,214].

Robotic devices can collaborate with movement, assist with movement and theoretically can also improve sensorimotor education[215]. An example of a task-specific robotic system that assists and collaborates with movement is the Lokomat® (Hocoma, Volketswil, Zurich, Switzerland) or robotic-assisted gait trainer (RAGT). RAGT has been safely used in children as young as 5 years of age with cerebral palsy. Children who have used RAGT show improved gait speed and Gross Motor Function Measurement (GMFM) dimension E (walking) scores[216]. Additional studies of RAGT have demonstrated improvements in maximum short-distance gait speed and dimension D (standing) of the GMFM after 3–5 weeks of RAGT[217]. Robotic ankle training is a more modest robotic therapy that can provide passive, active assist or active training for ankle range of motion. These robotic devices have been found to increase range of motion and to improve gait parameters in children with cerebral palsy[218–220]. The reports on both ankle and gait robotic devices are proof of concept only and lack control groups and randomization.

Virtual reality, including video games that offer motivating, full-body movement, is being embraced by rehabilitation practitioners worldwide. However, as these games were developed for recreational use, several challenges must be overcome before they can be effectively implemented in a clinical setting[221]. The cost of gaming set up, availability of in-home space as well as the child's time are considerations for in-home goal-directed virtual reality therapy.

Combining virtual reality with robotic-assisted movement devices increases participation in RAGT[222]. Virtual reality has been tested in balance disorder, perceptions and hemiplegia[223–226], but is not superior and has not been established compared to other more

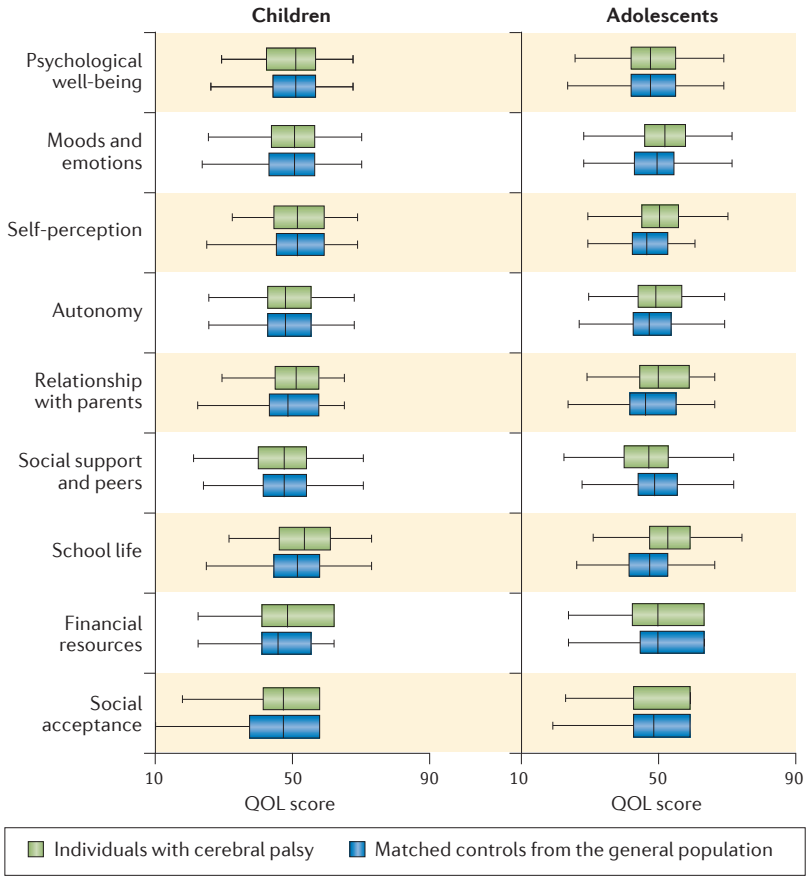

Figure 11 | **Quality-of-life scores by domain of the KIDSCREEN questionnaire.** Quality-of-live (QOL) domains affected by cerebral palsy in children and adolescents. Data collated from reports in REFS 238,239.

conventional therapies[227]. Research is needed to determine whether the motivational aspects of virtual reality systems will be sustained during longer and repeated sessions or if the novelty of virtual reality systems is part of the initial appeal that declines over time[228].

Currently, robotic assists have been centred on and used in extending therapy for children. However, telemedicine or tele-rehabilitation is gaining momentum so that home use is imminent and desirable. Children and families readily embrace novel technology treatments. However, for technology to be effective and sustained over time, it should be user friendly, lightweight, adaptable, efficient and cost effective with evidence to support use.

Management of non-motor symptoms

The care of both children and adults with cerebral palsy involves attention to numerous medical issues that may be present. Epilepsy occurs in approximately 40% of individuals with cerebral palsy, most commonly in those with severe motor impairment[229–231]. Obtaining a careful history of seizure type will enable the appropriate choice of anti-epileptic medication when indicated. Growth and nutrition should be monitored remembering that failure to thrive and undernutrition frequently occur owing to oro-motor difficulties. The use of gastrostomy feeding tubes can both improve nutrition and enhance QOL. Gastro-oesophageal reflux commonly occurs and can result in pain, poor appetite and, if severe, aspiration[232]. Chronic lung disease may develop in some individuals owing to aspiration from oro-motor dysfunction or gastro-oesophageal reflux. Respiratory complications are a major cause of morbidity and mortality[233]. Osteopaenia may require treatment, particularly following a pathological fracture[234]. Management of drooling with speech pathology interventions, medications, BoNT-A injections or surgery to the salivary glands can significantly enhance QOL[235].

Quality of life

Two crucial outcomes for all people, not just those with cerebral palsy, are 'QOL' — defined as "the individual's perception of their position in life in the context of the culture and value systems in which they live" (REF. 236) — and 'participation' — defined as "involvement in life situations" (REF. 237). QOL is, therefore, subjective and self-reported. Participation may be self-reported but seeks an objective account that could be externally validated.

Children and young people

The QOL of children and young people (8–17 years of age) with cerebral palsy is similar to that of their peers in the general population across nine domains of the KIDSCREEN instrument[238,239] (FIG. 11). By contrast, their participation in life activities is much reduced[240,241], by amounts that are proportional to the severity and number of disabilities.

In addition, QOL of adolescents with cerebral palsy is significantly reduced on the social support domain (that is, the child's perceived social support from peers and friends). QOL estimated from parent-proxy reports (including those with severe learning difficulties) is lower on some domains of QOL, and more-severe impairment is associated with lower QOL[242]. Careful interpretation is needed because stress that parents may experience raising a child with cerebral palsy may colour their judgement of their child's QOL[243]. Parents of children with cerebral palsy commonly experience stress and depression. Although services aim to minimize parental stress, they may inadvertently exacerbate it if poorly coordinated or limited resources require parents to struggle to obtain services. However, parental stress in childhood is only weakly associated with patient-perceived QOL during adolescence[239]. Although an able-bodied person might consider it stressful to raise a child with cerebral palsy and might view with dread having cerebral palsy themselves, life is not perceived in this way by individuals with cerebral palsy[238,239,244].

Pain is strongly associated with reduced QOL and reduced participation. At all ages, pain in individuals with cerebral palsy is more prevalent than in the general population[245–247]. Clinicians should ask their patients about pain and try to alleviate it when present. Where possible, causes of the pain should be eliminated (for example, gastro-oesophageal reflux) or avoided. Physiotherapy may cause pain; assisted stretching is

the daily activity most frequently associated with pain despite the fact that in neurological conditions such as cerebral palsy, stretching does not produce clinically important improvements in contractures or function[248]. If pain cannot be eliminated entirely and an individual develops chronic pain, strong evidence supports the benefit of distraction techniques, hypnosis or cognitive–behavioural therapy[249].

Adults

Although cerebral palsy is a lifelong condition, most research has regarded it as a paediatric issue. Recognition that outcomes in adulthood may be poor has highlighted the need to take the entire life course of the patient into account[250]. Little research has investigated QOL of adults with cerebral palsy. However, adults with cerebral palsy experience disadvantages in social life and employment[251,252]. Fatigue, pain and depressive symptoms are also common[253]. Looking at the disorder with a life-course perspective also highlights that the outcomes of QOL and participation during the phase when a young person transitions from child to adult services are not good[254], in part because paediatric services may fail to prepare young people for adult health care. Moreover, an adult has to balance choices between therapy, education, pain relief, employment and so on to suit them. Such independence should be encouraged during adolescence, rather than restricted by overly protective parents or clinicians.

Outlook

The outlook for individuals with cerebral palsy has improved dramatically over the past 30 years. For example, sophisticated brain imaging (MRI) has enabled some understanding of the neuropathology and timing of the brain injury[129]. The introduction of BoNT-A has substantially changed the treatment of spasticity[255], and intrathecal baclofen therapy has improved the comfort and care of those with both spasticity and dystonia[256]. There have been improvements in the treatment of the associated disorders, such as the enhanced range of medications for seizure control and the introduction of gastrostomy feeding devices that can improve health and nutrition[257]. Rehabilitation technology including voice output communication devices and powered wheelchairs have expanded the horizons and opportunities for people with cerebral palsy.

However, parents of children with cerebral palsy and individuals with cerebral palsy rightly demand more: improved treatments, better equipment, improved societal attitudes and, above all, a cure for the movement disorder. Is a cure on the horizon for cerebral palsy? Prevention — rather than cure — is the most realistic option[258]. There is a plethora of published work on risk factors, but more needs to be done. The introduction of cooling following neonatal encephalopathy[32] and the use of magnesium sulfate in women at risk of preterm birth for neuroprotection of the fetus[25] have resulted in profound reductions in the rates of cerebral palsy. Other interventions are likely to arise over the next decade.

Early identification and early interventions in cerebral palsy may improve outcomes. Studies directed at all preterm infants have failed to identify positive effects on motor development, possibly owing to the fact that these studies do not specifically target children with a high probability of developing cerebral palsy. This could be achieved by the evaluation of children at risk with a combination of neuroimaging and the General Movements Assessment[129–131]. A research agenda directed at large-scale identification of infants showing early signs of cerebral palsy followed by testing of high-intensity early interventions has been proposed[259].

Improved technology can considerably enhance the lives of individuals with cerebral palsy and further advances in this field are likely. Currently, equipment such as voice output communication devices are often difficult to program and may be challenging to use, particularly in the presence of profound motor impairment. Advances in eye-tracking technology may facilitate the ability to communicate for those without speech[260], and improved environmental control systems may enable more individuals to live independently.

Stem cells have been suggested as a treatment for cerebral palsy — in particular, human umbilical cord blood stem cells — with preclinical studies of brain injuries showing evidence of therapeutic potential. Transplantation of umbilical cord blood cells in acute animal models of cerebral palsy, such as excitotoxic white matter injury[261] and neonatal hypoxia–ischaemia[262], have shown profound functional improvement. Investigations into the mechanisms of umbilical cord blood stem cells reveal anti-inflammatory properties, protection of neural cells from secondary cell death, promotion of host cell proliferation and migration, and angiogenesis. Human stem cells do not seem to engraft and replace lost brain cells in immune-suppressed animal models[263–266]. Whether these mechanisms will operate in the same way in children with cerebral palsy who have had their injury some years previously is unclear[267–270]. Cerebral palsy is a heterogeneous condition with varied brain pathology and it is possible that stem cell infusions may act through varying mechanisms in different children. For example, some children have large brain lesions that might benefit from increasing the number of available neurons[271] and improvement in function may be due to the recruitment of endogenous stem cells following human umbilical cord blood infusion[272]. Some infants born preterm may have a reduced number of neural connections rather than a reduced number of neurons, and infused or endogenous stem cells may act to increase synapses and dendritic branching rather than generating new neurons from either infused or endogenous stem cells[273]. Alternatively, improving the neural support system by increasing white matter could enable functional improvement[269]. At this point, there is no evidence that stem cells cause either an increase in the number of neurons or neural connections in the human brain. The limited information available on the effects of infused stem cells on the human brain suggest increased perfusion[274] and metabolic activity[275,276] in some regions, as identified by single-photon emission CT and ^{18}F-fluorodeoxyglucose PET (with or without CT).

Magnetic resonance with diffusion tensor imaging has indicated some change in white matter tracts[274,275]. These effects varied considerable between individuals, and at this point the data are limited by small participant numbers.

No efficacy studies using stem cells in children with cerebral palsy have yet been published, but there are a few studies that have demonstrated safety[277] and imply potential efficacy of this intervention. Randomized, placebo-controlled crossover trials of autologous umbilical cord blood cells are underway in children with cerebral palsy[278,279]. Another trial compares the infusion of either autologous umbilical cord blood stem cells or autologous bone marrow mononuclear cells[280]. Each of these trials will evaluate safety and gross motor function, along with a range of secondary endpoints. MRI will be used to assess change in brain structure in two of the studies[278,280].

Randomized controlled trials of unrelated donor (allogeneic) cord blood have recently been reported. The first combined allogeneic cord blood with erythropoietin (a neuroactive potentiator) and rehabilitation compared with controls receiving placebo, erythropoietin and rehabilitation and controls receiving placebo and rehabilitation — with 31 participants in each group[275]. The second trial compared allogeneic cord blood combined with rehabilitation against placebo and rehabilitation (17 participants in each group)[281]. In both trials, the cord blood treatment groups showed benefit at 6 months after infusion on several mental and motor assessment scales. As all groups were reported to have changed and the studies were underpowered, it is not clear to what extent observed changes were a function of developmental progress and thus distinct from the effects of the interventions. Further trials are proceeding in Korea. A randomized comparative trial involving intrathecal infusion of mesenchymal stem cells derived from allogeneic cord blood with either 1 year of rehabilitation therapy or with standard clinical care has recently commenced in China[282].

The accumulating preclinical evidence of the therapeutic value of human umbilical cord blood stem cell therapy, together with safety evidence from clinical trials, has led to increasing media coverage and has created hope and expectations of a cure among families and also professionals[283]. However, the literature evidence regarding efficacy is mixed and clinical data are scarce.

In the next few years, the role of stem cell therapy for cerebral palsy will be clarified as further studies are undertaken to determine efficacy and the best stem-cell type, in addition to determining dose and the most appropriate mode of delivery. Neurorehabilitation will remain the central treatment combined with tone management, treatment of medical issues, orthopaedic surgery when indicated and promotion of inclusion and best QOL. If stem cells have the potential to enrich the nervous system, they may add to the therapeutic options available to facilitate functional gains, even if they cannot achieve a cure.

In the meantime, parents and individuals with cerebral palsy must be cautioned that, despite our hopes and aspirations for these young people and their families, a cure is not imminent. Helping them to achieve optimal outcomes and the best possible participation in every aspect of community life must continue to be the prime goal while researchers work on more long-term solutions.

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Author contributions

Introduction (P.R.); Epidemiology (N.P.); Mechanisms/pathophysiology (B.D., R.L.L. and J.-P.L.); Diagnosis, screening and prevention (D.S.R., P.R. and H.K.G.); Management (J.-P.L., D.L.D., H.K.G., J.G.B. and D.G.-S.); Quality of life (A.C.); Outlook (D.S.R. and K.E.C.); Overview of Primer (P.R. and H.K.G.).

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