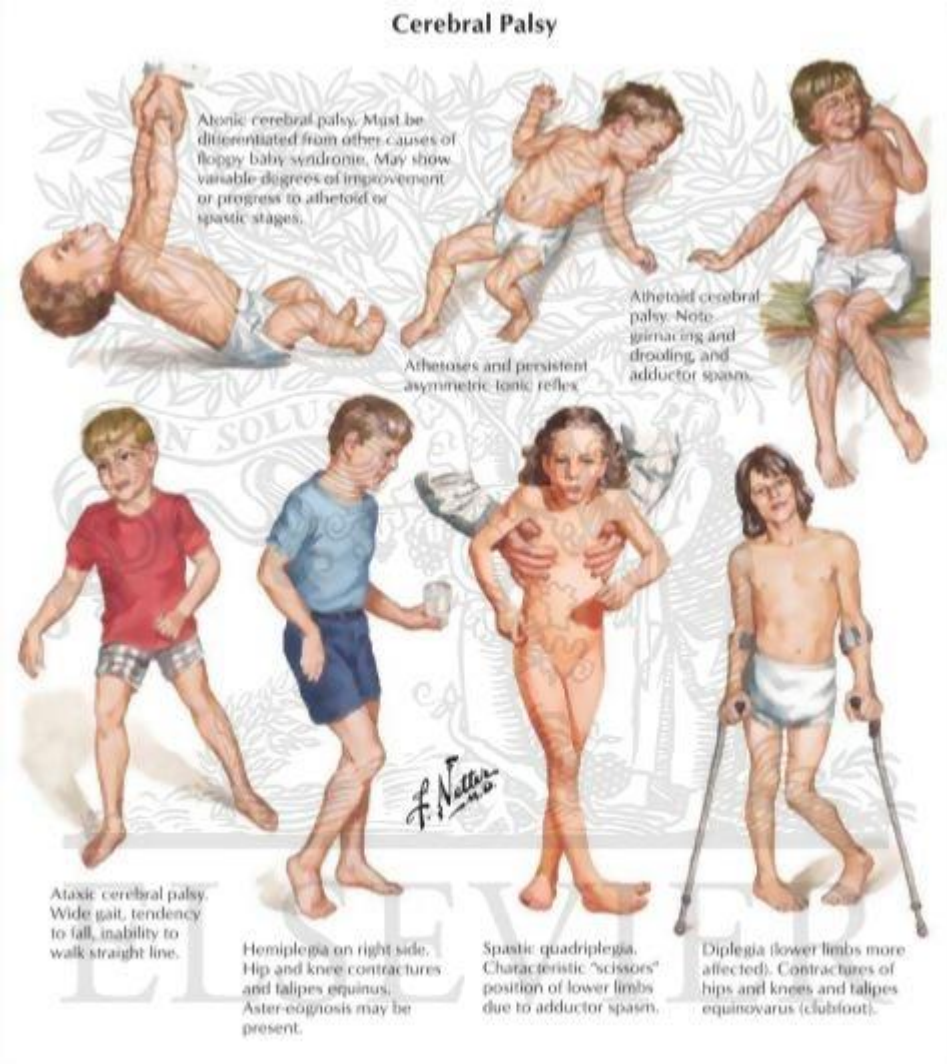
PARALISI CEREBRALE INFANTILE 2022



"Cerebral palsy describes a group of permanent disorders of the development of movement and posture, causing activity limitations that are attributed to non-progressive disturbances that occurred in the developing foetal 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."
(Dev Med Child Neurol Suppl 2007; 109: 8 – 14)

PREVALENZA

Nei paesi sviluppati 2 – 2,8 per mille nati
Nei paesi in via di sviluppo 1,5 – 5 per mille nati vivi

Neuropsychiatric Disease and Treatment 2020:16

Importanza della diagnosi!!!

Quale è/sono la/le causa/e della PCI

Risk factors

Although numerous risk factors for CP have been identified, many children with these risk factors (for example, premature birth) do not go on to develop CP, and nearly 50% of children who are ultimately diagnosed with CP are term-born children who have no identified risk factors in the neonatal period [24].

McIntyre S, Morgan C, Walker K, et al. Cerebral palsy–don't delay. Dev Disabil Res Rev 2011;17(2):114–29.

Table 1: Risk factors for cerebral palsy [2, 7, 10].

Preconception	Before birth	During birth	After birth
Systemic illness of the mother	Premature birth	Premature birth	Hypoxic ischemic encephalopathy
Use of drugs and stimulants	Low birth weight	C-section	Infection
Immune system disorders preceding pregnancy	CNS malformation	Vacuum-assisted delivery	Hyperbilirubinemia
Spontaneous abortions	Maternal DM	Delivery after the due date	Cerebrovascular accidents
Socioeconomic factors	Prolonged rupture of membrane	Prolonged labor	Intracranial hemorrhage
Poisoning	Maternal hemorrhage	Asphyxia	CNS infection
Infections	Multiple gestations	Meconium aspiration	Respiratory distress syndrome
Impaired fertility	Cotwin death	Breech vaginal delivery	Artificial respiratory support
Treatment of fertility	Genetic factors	A high fever during delivery	Hypoglycemia neonatal convulsions
	Encephalopathy of prematurity		Traumatic brain injury
	Congenital malformation		Near drowning
	Hypoxic ischemic encephalopathy		Meningitis
	In utero stroke		Sepsis
Genetic factor	In vitro fertilization	Perinatal stroke	
	Kernicterus		
	Maternal disorder of clotting		Neonatal encephalopathy
	Meconium aspiration		
	Fetal growth restriction		
	Preeclampsia		

Oxidative Medicine and Cellular Longevity
Volume 2022, Article ID 2622310, 20 pages
https://doi.org/10.1155/2022/2622310

Hindawi
Oxidative Medicine and Cellular Longevity
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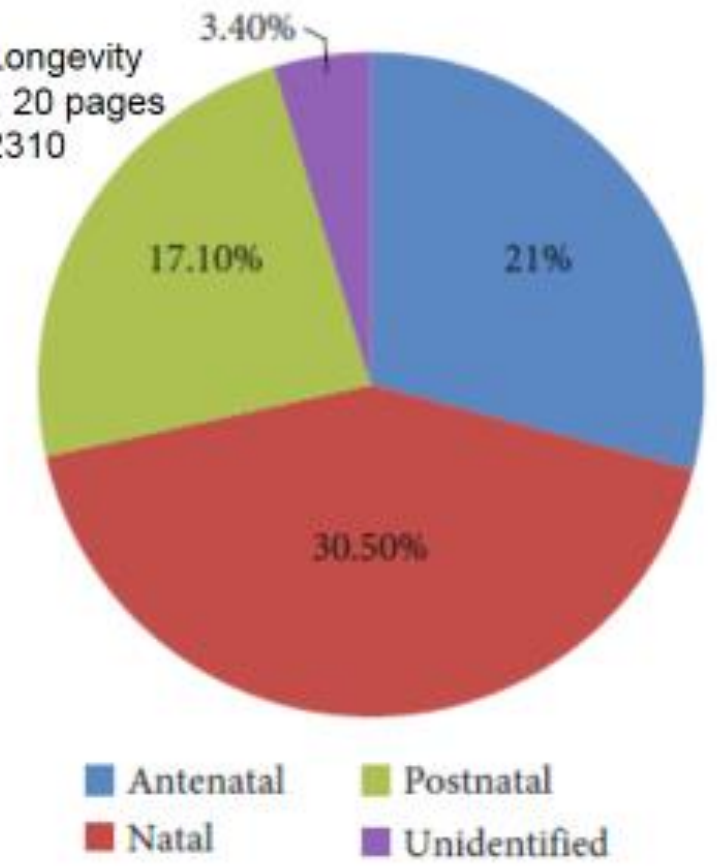


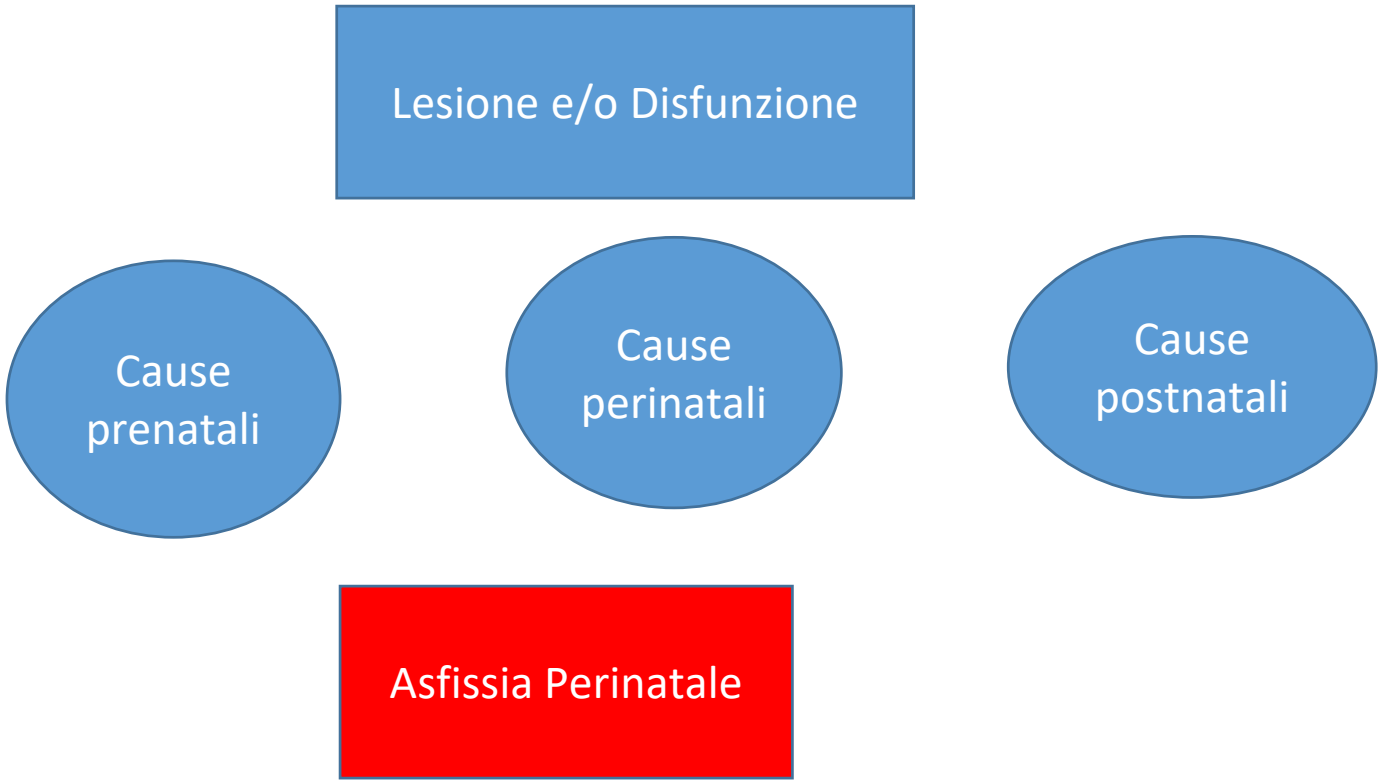
FIGURE 1: Risk factors for cerebral palsy [2, 7, 10].

Table 2: Etiologies of cerebral palsy [2, 8, 11–13, 15].

Prenatal	Perinatal	Postnatal
Infection and fever during pregnancy	Obstructed labor	Hypoglycemia
Metabolic disorders	Cord prolapses	Jaundice
Intrauterine infection	Antepartum hemorrhage	Neonatal meningitis
Chorioamnionitis	Metabolic acidosis	Septicemia
Maternal ingestion of toxins	Use of assisted reproductive technology	Malaria
Preeclampsia		Malaria with seizures
Maternal trauma in pregnancy		Malaria with coma
Exposure to methylmercury		
Genetic syndromes		Meningitis
Multiple pregnancies		
IUGR		Tuberculosis
Fetal growth restriction	Intrapartum hypoxia	Sickle cell disease
Placenta abruption		HIV
Failure of closure of the neural tube		PVL
Schizencephaly		Congenital infections
Chromosomal defects		Asphyxia
Microcephaly		Hyperbilirubinemia
Rubella	Oxidative Medicine and Cellular Longevity	Genetic causes
		Neonatal stroke

PATOGENES
I

Multifattoriale e non completamente conosciuta



Panel: Criteria proposed by the International Cerebral Palsy Task Force to define an acute intrapartum hypoxic event

Essential criteria

1. Evidence of a metabolic acidosis in intrapartum fetal, umbilical arterial cord, or very early neonatal blood samples (pH <7·00 and base deficit ≥12 mmol/L)
2. Early onset of severe or moderate neonatal encephalopathy in infants of ≥34 weeks' gestation
3. Cerebral palsy of the spastic quadriplegic or dyskinetic type

Criteria that together suggest an intrapartum timing but by themselves are nonspecific

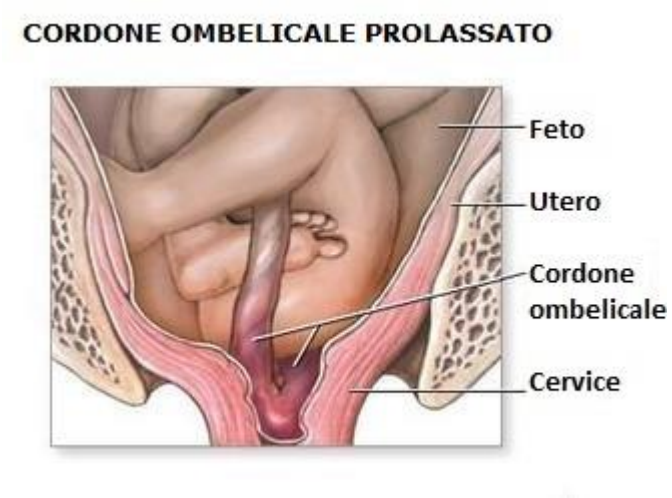
4. A sentinel (signal) hypoxic event occurring immediately before or during labour
5. A sudden, rapid, and sustained deterioration of the fetal heart rate pattern, usually after the hypoxic sentinel event, where the pattern was previously normal
6. Apgar scores of 0–6 for longer than 5 min
7. Early evidence of multisystem involvement
8. Early imaging evidence of acute cerebral abnormality

Reproduced from MacLennan,[11] by permission of the BMJ Publishing Group.

2 -10 % dei casi di PCI

Apgar
Monitoraggio battito cardiaco fetale
Emogas analisi del sangue
del cordone ombelicale

Anomalie placentari
Cisti e/o Calcificazioni cerebrali



Platt and colleagues (2017)
found that a prenatal cause was most likely to be responsible for
about 50% to 55% of quadriplegic CP, a perinatal cause in 30%, and a postnatal
cause in 15% to 20%. Different brain structures show varying levels of susceptibility
to insult or injury at different gestational ages, which further supports
the idea that CP can develop at any point through pregnancy caused by multiple
injuries throughout development. Despite advances in diagnostic techniques,
a specific cause is found for no more than 50% to 75% of CP cases.

PCI è associata all'età gestazionale

Prevalenza nei nati a termine 1/40
rispetto alla prevalenza nei nati estremamente pretermine

Tasso pretermine negli US dal 9,1% nel 1983 a 12,3% nel 2003

Late preterm (34 sett e 0/7 giorni – 36 sette 6/7gg)
74% di tutti i pretermine e l'8% di tutte le nascite

Sopravvissuti nati prima della 28° settimana solo lo 0,4%

Maggior parte degli studi EG <28 sett - <32

96% dei nati alla 35° sett e oltre 2/3 delle PCI

Himmelmann et al.

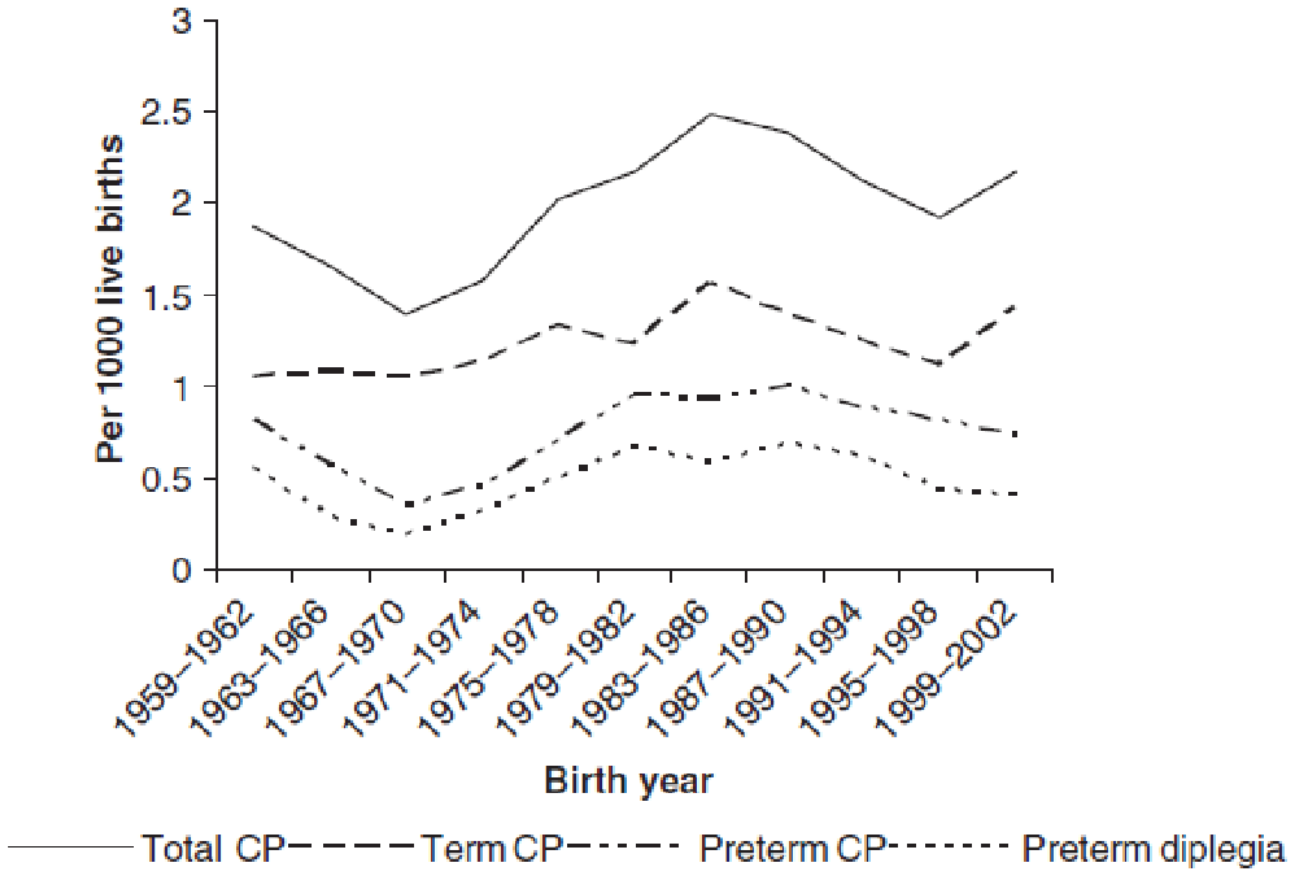


Figure 2 Crude prevalence of CP per 1000 live births in the birth years 1959–2002.

The changing panorama of cerebral palsy in Sweden. X. Prevalence and origin in the birth-year period 1999–2002

K Himmelmann (kate.himmelmann@vgregion.se), G Hagberg, P Uvebrant

2010 Foundation Acta Pædiatrica/*Acta Pædiatrica* 2010 **99**, pp. 1337–1343

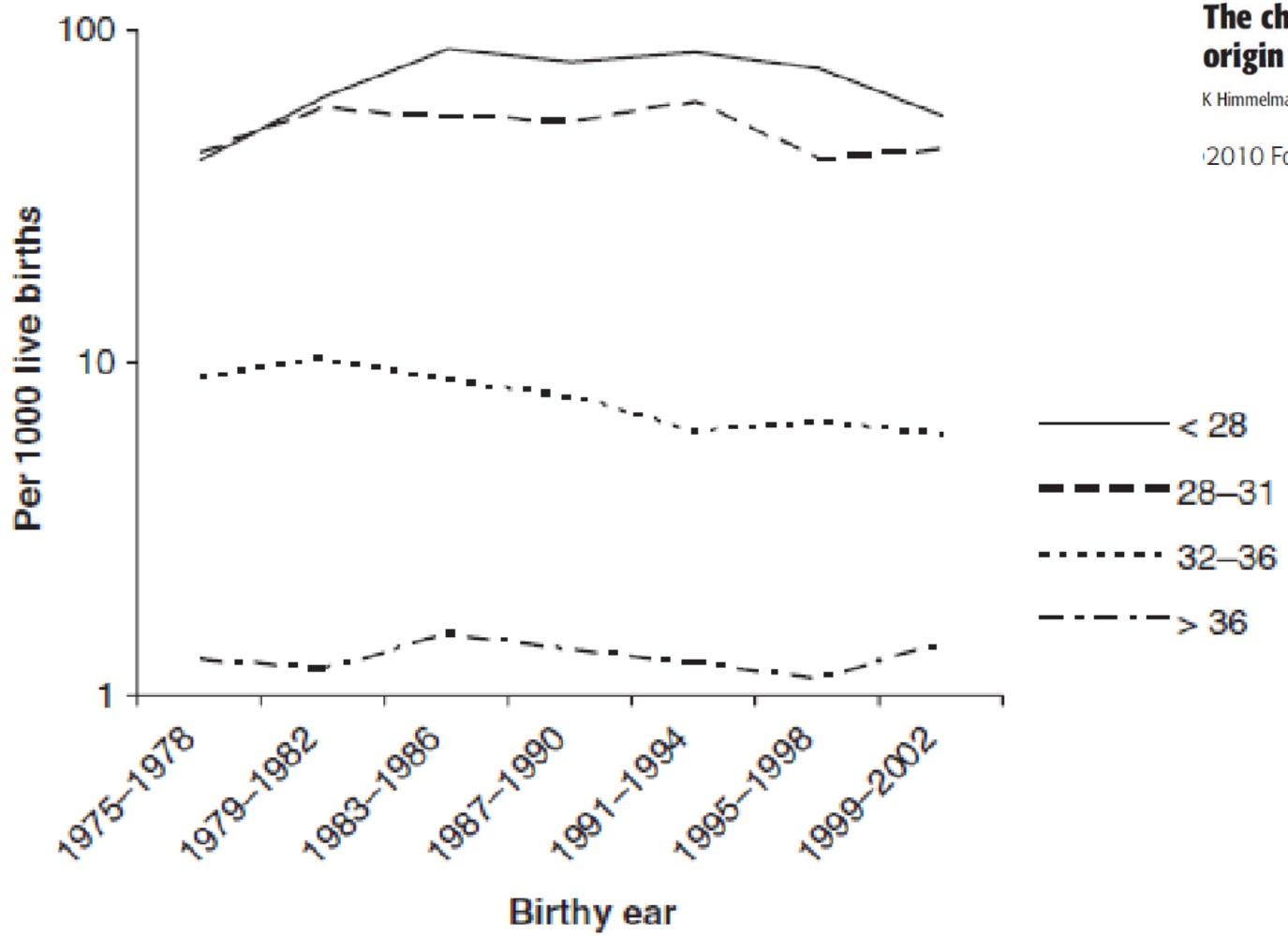


Figure 3 Prevalence of CP by gestational age, 1975–2002.
[Correction added after online publication: the y-axis of figure 3 was corrected]

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Review

Reprint of "The developing oligodendrocyte: key cellular target in brain injury in the premature infant"☆

Joseph J. Volpe[a,*], Hannah C. Kinney[b], Frances E. Jensen[a], Paul A. Rosenberg[a]

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[b] Department of Pathology, Children's Hospital and Harvard Medical School, Boston, MA 02115, USA

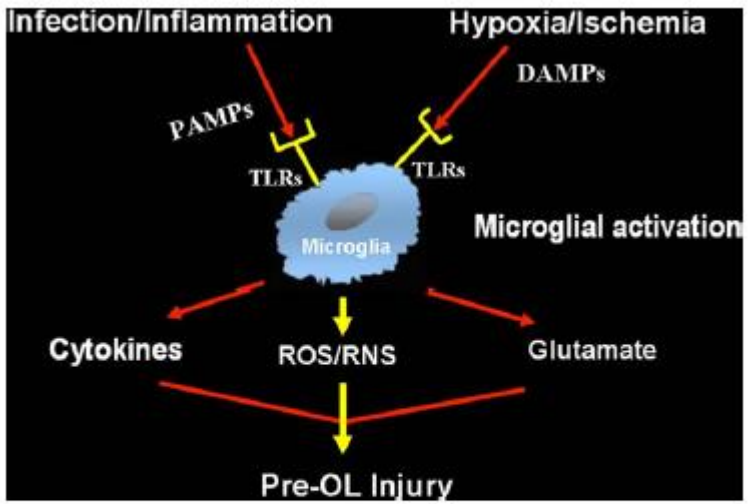

Fig. 12. Microglia and innate immune mechanisms in pre-OL injury. Microglia may act as a convergence point for both upstream mechanisms in PVL, i.e., systemic infection/inflammation and hypoxia-ischemia, and innate immunity is likely involved in both microglial mechanisms. Thus, pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), respectively lead to microglial activation and resulting release of products, especially reactive oxygen and nitrogen species (ROS/RNS) and cytokines, that result in pre-OL injury. See text for details.

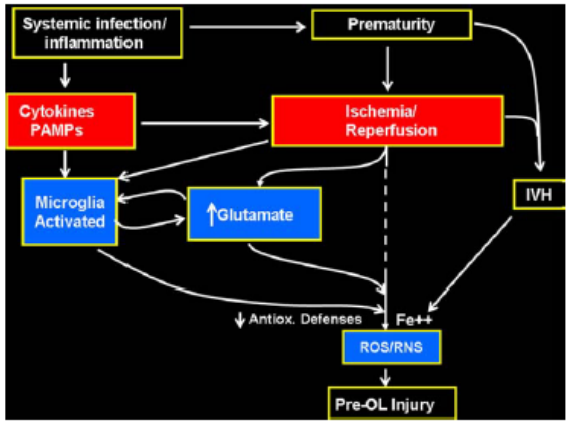

Fig. 6. Pathogenesis of PVL. The two major upstream mechanisms (red) are ischemia and systemic infection/inflammation, activating three major downstream mechanisms (blue), microglial activation, glutamate excitotoxicity and ultimately, free radical attack. See text for details. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

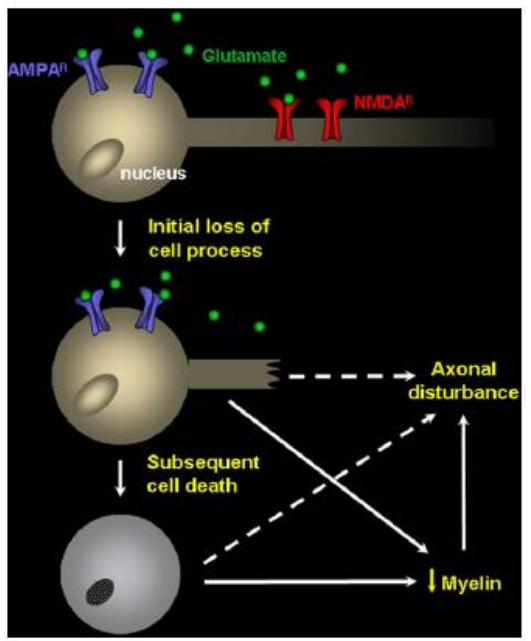

Fig. 11. Potential differential effects and temporal aspects of excitotoxicity to developing oligodendrocytes. The intact cell (*top*) has AMPA receptors primarily on the cell soma and NMDA receptors primarily on the cell processes. Initially with excess extracellular glutamate, activation of NMDA receptors could lead to loss of cell processes, and if excitotoxicity continues, to activation of AMPA receptors and cell death. Either event could lead to impaired myelination (*solid arrows*) and potentially also to axonal disturbance (*dotted lines*).

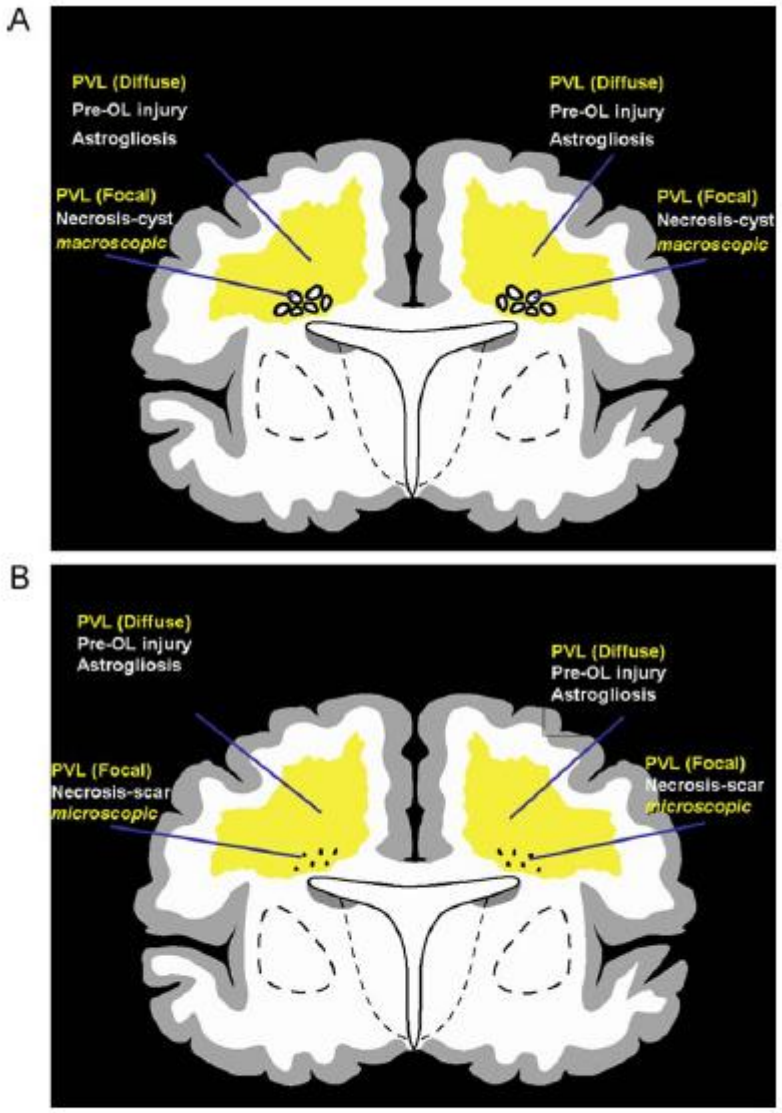

Fig. 3. Cystic (A) and noncystic (B) periventricular leukomalacia (PVL) – schematic diagrams. (A) Cystic PVL is characterized by macroscopic (several mm or more) focal necrotic lesions that become cystic and by diffuse astrogliosis and pre-OL injury. (B) Noncystic PVL is characterized by focal necrotic lesions that are *microscopic* and evolve principally to small glial scars rather than cysts.

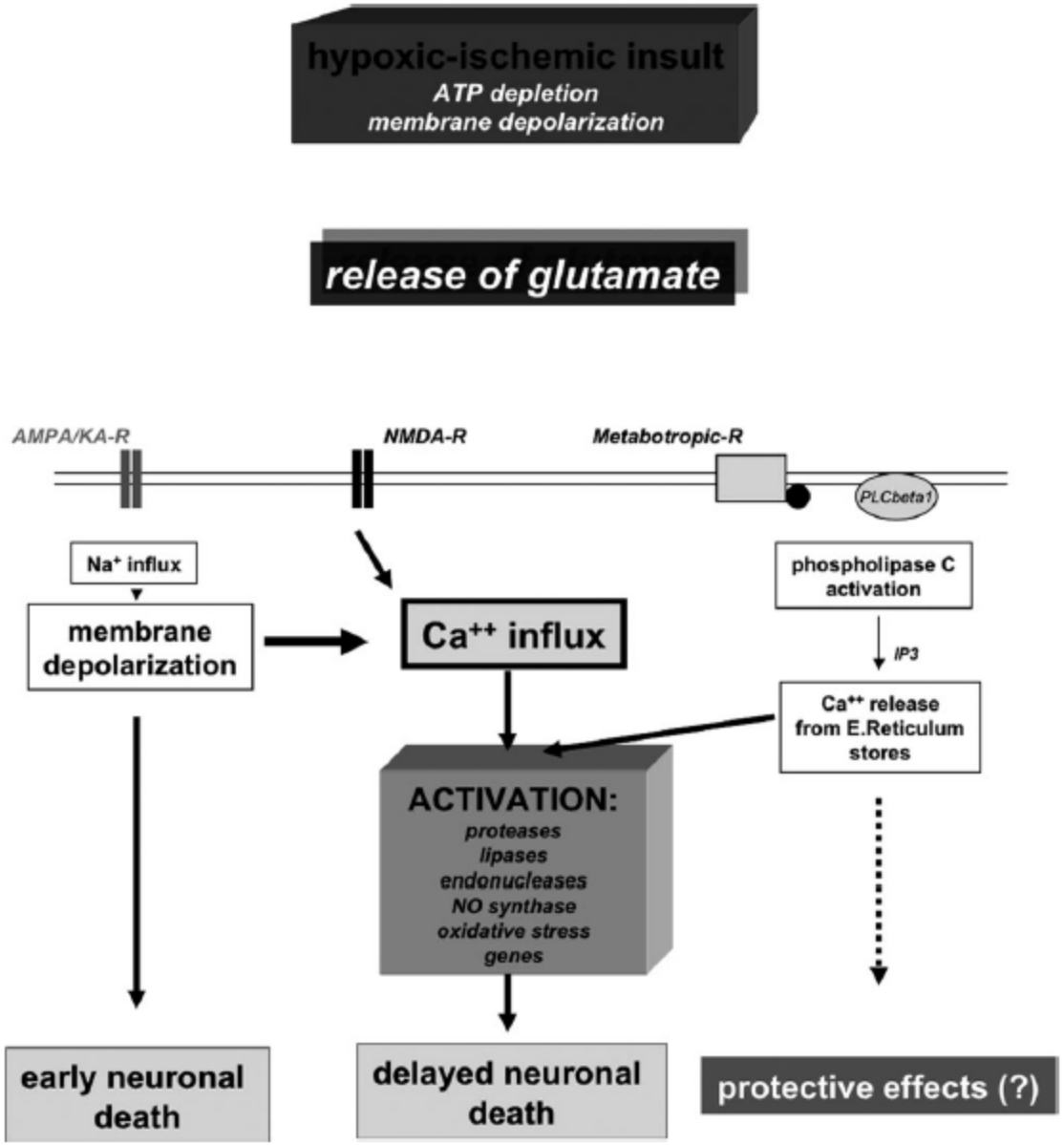

Figure 3. Diagram of the molecular cascade leading to neuronal cell death after perinatal hypoxic–ischemic insult in term newborns. R = receptors.

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Molecular Mechanisms Involved in Injury to the Preterm Brain

Angela M. Kaindl, MD, **Géraldine Favrais, MD**, and **Pierre Gressens, MD, PhD**
Inserm, U676, Paris, France (AMK, GF, PG); Université Paris 7, Faculté de Médecine Denis Diderot, Paris, France (AMK, GF, PG); PremUP, Paris, France (AMK, GF, PG); AP HP, Hôpital Robert Debré, Service de Neurologie Pédiatrique, Paris, France (PG)

Table 1
Risk Factors for the Development of Encephalopathy of Prematurity

Antenatal Factors	Perinatal Factors	Postnatal Factors
Inflammation	Hypoxia-ischemia	Oxidative stress
Hypoxia-ischemia	Excitotoxicity	Inflammation
Toxins	Oxidative stress	Pain
Malnutrition	Loss of maternal GF	Excitotoxicity
Maternal stress	Drugs	Drugs
Genetic factors	Genetic factors	Loss of maternal GF
		Genetic factors

GF, growth factor.

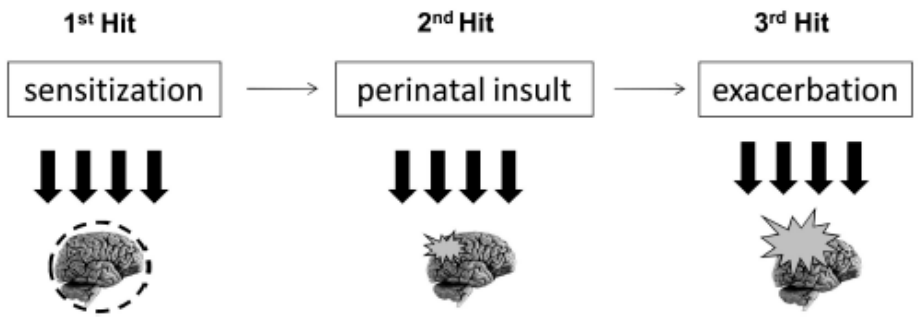

Figure 1.
Multiple-hit hypothesis for the development of encephalopathy of prematurity. Schematic representation illustrates the multiple-hit hypothesis, including pre-, peri-, and postnatal factors.

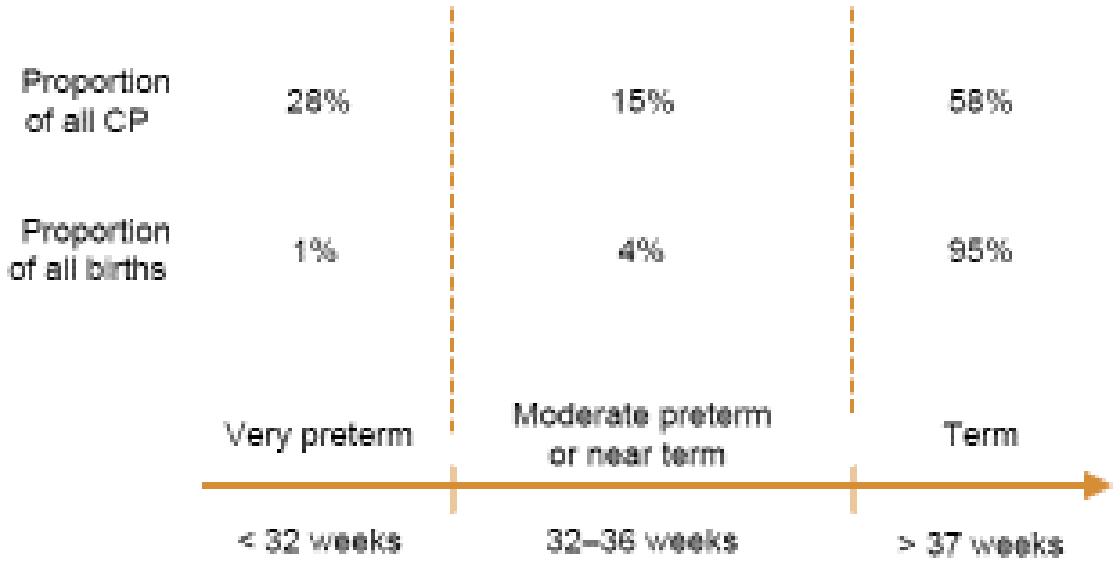

Figure 2. Proportion of CP according to gestational age (data from ref. 2).

Nelson & Blair (2015) segnalano l'importanza dei "Birth Defects"(BD) Con questo termine essi si riferiscono alle "congenital malformations" di altri autori senza differenziare tra malformazioni maggiori e minori.

In uno studio di popolazione di neonati – lattanti affetti da encefalopatia neonatale, il 27,5% aveva BD rispetto al 4,3% dei controlli.

...

Nello studio SCPE il 12% dei bambini affetti da PCI, aveva malformazioni cerebrali

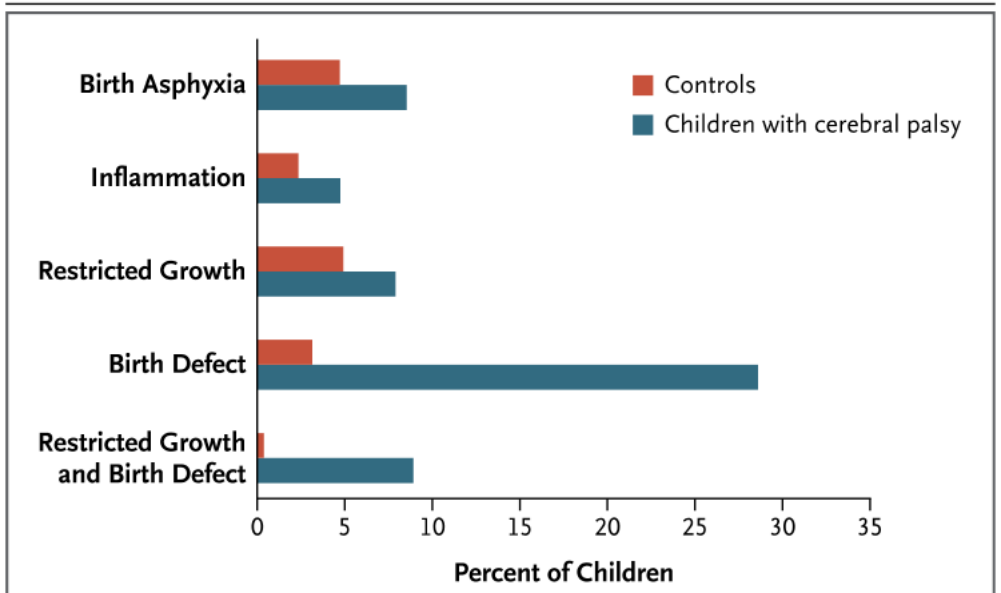

Figure 2. Distribution of Four Major Risk Factors in Singleton Children with Cerebral Palsy Born at a Gestational Age of at Least 35 Weeks, 1980–1995.

Data are from a study of 496 children with cerebral palsy and 508 controls. The four risk factors were a potentially asphyxiating intrapartum event, evidence of inflammation, fetal growth restriction (defined as a birth weight that was more than 2 SD below the optimal weight for gestation, sex, maternal height, and parity, or a neonatal diagnosis of fetal growth restriction), and a major birth defect. Data shown are for one or more of these risk factors in at least 2% of children with cerebral palsy or controls. Major birth defects were the most frequently occurring risk factor in children with cerebral palsy, and when combined with fetal growth restriction, they were associated with the highest relative risk.

Genomic insights are a gateway to understanding the neurogenetic routes that cause CP and have the potential to influence patient care. Suspicion of CP's genetic basis stems from its syndromic presentations and its association with twinning (especially the monozygotic variant), consanguinity, and congenital anomalies [61–63]. Human genome sequencing, including whole-exome sequencing, X-chromosome exome sequencing, and chromosomal analysis in population studies, has led to the identification of various gene mutations that are linked to the development of CP, indicating that no single CP gene exists but that multiple genes are involved [64,65]. This genetic heterogeneity underscores the complexity of the contribution of genes to the development of CP.

Neuromol Med (2014) 16:821–844
DOI 10.1007/s12017-014-8331-9

ORIGINAL PAPER

A Diagnostic Approach for Cerebral Palsy in the Genomic Era

Ryan W. Lee · Andrea Poretti · Julie S. Cohen · Eric Levey · Hilary Gwynn · Michael V. Johnston · Alexander H. Hoon · Ali Fatemi

Table 1 Clinical and imaging red flags in patients with suspected cerebral palsy

1. Normal MRI findings
2. Imaging abnormalities isolated to the globus pallidus
3. Severe symptoms in the absence of a history of perinatal injury
4. A pattern of disease inheritance, or consanguinity
5. Neurodevelopmental regression, or progressively worsening symptomatology
6. Isolated muscular hypotonia
7. Rigidity (as opposed to spasticity) on physician examination
8. Paraplegia

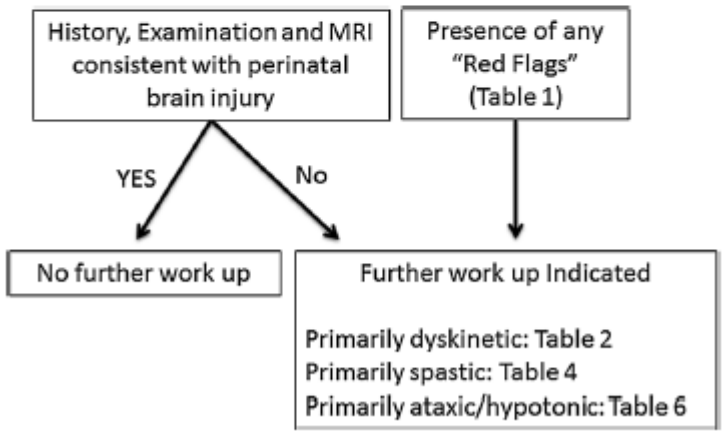

Fig. 1 Diagnostic evaluation of the child with cerebral palsy

Table 2 Neurogenetic disorders masquerading as dyskinetic cerebral palsy

Dyskinetic disorders	Gene(s)[a]	Distinctive characteristics[b]	Neuroimaging findings	Diagnostic tests	Treatment[d]
Aromatic acid decarboxylase deficiency	*DDC*	Oculogyric crises, autonomic dysfunction, ptosis, athetosis	None	CSF study (Table 3), blood enzyme assay, genetic analysis	Pyridoxal phosphate, folinic acid, pramipexole
Dopa-responsive dystonia	*GCH1*	Progressive dystonia, low CSF biopterin and neopterin	None	CSF study, genetic analysis	Levodopa
Pantothenate kinase-associated neurodegeneration	*PANK2*	Progressive dystonia	Bilateral globus pallidus hyperintensity with hypointensity in the anterior/lateral region (eye of the tiger)	Neuroimaging, genetic analysis	None
Monocarboxylate transporter 8 deficiency	*SLC16A2*	GDD/ID, hypotonia, dystonia, high T3, low T4, normal TSH	White matter hyperintensity	High T3, rT3 levels, genetic analysis	None
Glutaric aciduria type 1	*GCDH*	Macrocephaly, dystonia	Frontotemporal atrophy, caudate and putamen hyperintensity and atrophy, temporal cysts	Organic acid analysis, enzymatic analysis, genetic analysis	Carnitine and choline; lysine restriction
Succinic semialdehyde dehydrogenase deficiency	*ALDH5A1*	Progressive dystonia, seizures, GDD/ID	Bilateral globus pallidus, dentate, subthalamic nuclei, and subcortical white matter hyperintensity	Organic acid analysis, enzymatic analysis, genetic analysis	None
Lesch–Nyhan syndrome	*HPRT1*	Cognitive delay, self-mutilation, hyperuricemia, dystonia	None	Serum uric acid, enzymatic analysis, genetic analysis	None
Wilson's disease	*ATP7B*	Hepatic disease, psychosis, Kayser–Fleischer rings, dystonia	Putamen, thalami, substantia nigra hyperintensity (panda sign), cerebellar atrophy	Low ceruloplasmin in serum, increased urinary excretion of copper, genetic analysis	Penicillamine, trientine hydrochloride
Glucose transporter 1 deficiency	*SLC2A1*	GDD/ID, seizures, ataxia, microcephaly, chorea, dystonia	None	Low CSF Glucose, genetic analysis	Ketogenic diet
Non-ketotic hyperglycinemia	*GLDC*	Developmental regression, seizures, apnea, lethargy	White matter hyperintensity, agenesis corpus callosum	High CSF glycine, genetic analysis	None; consider ketamine
Propionic acidemia	*PCCA, PCCB*	Encephalopathy, GDD/ID, hyperammonemia, seizures	Globus pallidus hyperintensity	Urine organic acid or acylcarnitines analysis, enzymatic analysis, genetic analysis	Caline, isoleucine, methionine, and threonine restriction
Leigh syndrome	*SURF1* and many more	Progressive dystonia, relapsing encephalopathy, vision and hearing loss, vomiting, seizures	Basal ganglia, cerebellum (dentate nuclei) and brainstem hyperintensity	Neuroimaging, genetic analysis	None
Pontocerebellar hypoplasia type 2	*TSEN54*	Chorea, dystonia, progressive microcephaly	Cerebellar atrophy (hemispheres > vermis), flat pons, thin corpus callosum, delayed myelination	Neuroimaging, genetic analysis	None
Maple syrup urine disease	*BCKDHA-B, DBT, DLD*	GDD/ID, dystonia, hypotonia, sweet smelling urine	Myelinated white matter, basal ganglia, and thalamic hyperintensity	Plasma amino acids analysis, enzymatic analysis	Avoid branched chain amino acids

[a] Gene(s) most commonly associated with disease

[b] Salient disease characteristics. *GDD/ID* global developmental disability/intellectual disability

[c] Magnetic resonance imaging findings that may assist in characterization of disease. Intensity is discussed with respect to T2-weighted image sequences

[d] Potentially disease modifying or curative treatment, not including supportive therapy

Table 4 Neurogenetic disorders masquerading as spastic cerebral palsy

Spastic disorders	Gene(s)[a]	Distinctive characteristics[b]	Neuroimaging findings[c]	Diagnostic tests	Treatment[d]
Holoprosencephaly	*SHH, TGIF1, SIX3, ZIC2*	Midline anomalies, GDD/ID, seizures, endocrine problems	Varied degrees of incomplete hemispheric separation	Neuroimaging, genetic analysis	None
Schizencephaly	*COL4A1*	GDD, seizures, hemi- or quadriparesis, microcephaly	Hemispheric cleft lined by heterotopic gray matter	Neuroimaging	None
Lissencephaly	*LIS1* (*PAFAH1B1*)	GDD/ID, seizures	Smooth gyral-sulcal pattern, 4 cortical layers instead of 6, cerebellar and pontine hypoplasia in some (TUBA1A, RELN)	Neuroimaging, genetic analysis	None
Hemimegalencephaly	*PIK3CA, AKT3, MTOR*	Macrocephaly, seizures, GDD/ID, hemiparesis	Unilateral enlarged cerebral hemisphere with ipsilateral cortical dysplasia, white matter signal abnormality, ventriculomegaly	Neuroimaging, genetic analysis	Hemispherectomy
Septo-optic dysplasia spectrum	*HESX1*	Vision, cognitive, and pituitary problems, seizures, nystagmus	Optic nerve hypoplasia, absent septum pellucidum	Neuroimaging	None
Polymicrogyria	*WDR62*	GDD/ID, seizures, hemi- or quadriparesis	Shallow sulci, thick cortex, many small cortical folds packed tightly together	Neuroimaging, genetic analysis	None
Aicardi Goutières syndrome	*TREX1, RNASEH2A-C, SAMHD1*	Developmental regression, sterile pyrexia, chilblains, microcephaly, hepatomegaly	Basal ganglia and white matter calcification, periventricular white matter hyperintensity, cerebral atrophy	Neuroimaging, CSF interferon study, genetic analysis	None
X-linked hydrocephalus with aqueductal stenosis	*L1CAM*	GDD/ID, upward gaze palsy, adducted thumbs, spastic paraparesis	Stenotic aqueduct of Sylvius, hydrocephalus, tectum dysplasia	Neuroimaging, genetic analysis	Endoscopic third ventriculostomy
Agenesis of the corpus callosum	None	GDD/ID, midline dysmorphology	Agenesis corpus callosum, lipoma and interhemispheric cysts occasionally	Neuroimaging	None
Pelizaeus–Merzbacher disease (and PMD-like disease)	*PLP1, GJA12*	GDD/ID, dystonia, seizures, nystagmus, spasticity, stridor	Hypomyelination	Neuroimaging, genetic analysis	None
Krabbe disease	*GALC*	Hypotonia, macrocephaly, developmental regression, progressive spasticity	Demyelination (posterior predominance and cerebellar white matter), thalamic hyperintensity	Enzymatic analysis, genetic analysis	None
Alexander disease	*GFAP*	Developmental regression, seizures, spasticity, macrocephaly	Demyelination with frontal and brainstem predominance, thalamic and basal ganglia hyperintensity, rim of periventricular hypointensity	Neuroimaging, genetic analysis	None
Hereditary spastic paraplegias	*SPG, L1CAM, ATL1*	Progressive spastic paraplegia, GDD/ID, cataracts, ataxia	In some types thin corpus callosum (e.g., SPG11) or cerebellar atrophy (e.g., SPG7)	Genetic analysis	None

Table 4 continued

Spastic disorders	Gene(s)[a]	Distinctive characteristics[b]	Neuroimaging findings[c]	Diagnostic tests	Treatment[d]
Arginase deficiency	*ARG1*	Spastic diplegia, GDD/ID, hyperammonemia	None; occasional cerebral atrophy	Plasma arginine level, genetic analysis	None
RNASET2-deficiency	*RNASET2*	Microcephaly, GDD/ID, seizures, hearing impairment	Multifocal cystic and calcified white matter lesions, temporal cysts	Genetic analysis	None
Mitochondrial DNA depletion syndrome	*MT-TK2, POLG1*	Seizures, hepatorenal failure	Basal ganglia, dentate hyperintensity, cerebellar atrophy	Genetic analysis	Folate
Hyperekplexia	*GLRA1, SLC6A5*	Exaggerated startle, truncal hypertonia	None	Clinical findings, genetic analysis	Clonazepam, Levetiracetam
Purine nucleoside phosphorylase deficiency	*PNP*	Immune deficiency, autoimmune disorders, GDD/ID	Multifocal leukoencephalopathy, stroke	Genetic analysis	Bone marrow transplant
Sjogren–Larsson syndrome	*ALDH3A2*	Ichthyosis, spastic diplegia, GDD/ID, myopia	Non-progressive white matter T2 hyperintensity	Abnormal leukotriene metabolites in urine, genetic analysis	None
Homocystinuria	*CBS, MTHFR*	GDD/ID, tall stature, seizures, myopia, ectopia lentis	Stroke, basal ganglia and white matter hyperintensity	Plasma total homocysteine level, genetic analysis	Vitamin B6
Pseudo-TORCH syndrome	None	Microcephaly, GDD/ID, seizures, spasticity	Periventricular calcifications, atrophy, polymicrogyria, simplified gyration	Neuroimaging	None
Sulfite oxidase deficiency/ molybdenum cofactor deficiency	*SUOX*	GDD/ID, seizures, axial hypotonia with peripheral hypertonia	White matter and basal ganglia hyperintensity, cerebellar hypoplasia, cystic encephalomalacia	Urine sulfites, Plasma and urine amino acids and urine organic acids study, genetic analysis	None

[a] Gene(s) most commonly associated with disease

[b] Salient disease characteristics. *GDD/ID* global developmental disability/intellectual disability

[c] Magnetic resonance imaging findings that may assist in characterization of disease. Intensity is discussed with respect to T2-weighted image sequences

[d] Potentially disease modifying or curative treatment, not including supportive therapy

Table 6 Neurogenetic disorders masquerading as ataxic/hypotonic cerebral palsy

Disorder	[a]Gene(s)	[b]Distinctive characteristics	[c]Neuroimaging findings	Diagnostic tests	[d]Treatment
Ataxia-Telangiectasia	*ATM*	Immune deficiency, ocular motor apraxia, telangiectasia, ataxia	Pure cerebellar atrophy	Serum alpha-feto protein, intracellular ATM protein	None
Congenital vitamin E deficiency	*TTPA*	Ataxia, sensory neuropathy	None	Vitamin E level, genetic analysis	Vitamin E
Dandy-Walker malformation	*FOXC1, ZIC1, ZIC4, FGF17*	Hydrocephalus, ataxia, GDD/ID	Cystic dilatation of the fourth ventricle, hypoplasia of the cerebellar vermis	Neuroimaging	Neurosurgical shunting
Joubert syndrome	*NPHP1, AHI1, CEP290*	Ataxia, ocular motor apraxia, GDD/ID	Molar tooth sign, hypoplasia and dysplasia of the cerebellar vermis	Neuroimaging	None
Niemann pick disease type C	*NPC1, NPC2*	Ataxia, vertical gaze palsy, regression, hepatosplenomegaly, psychiatric problems	Periventricular white matter hyperintensity, cerebral and cerebellar atrophy	Filipin test, genetic analysis	None
MELAS syndrome	*MT-TL1, MT-ND5, MT-TH*	Seizures, ataxia, cognitive delay, lactic acidosis, strokes	Stroke (primarily occipital), cerebellar atrophy	Genetic analysis	None; consider CoQ10, riboflavin
Coenzyme Q10 deficiency	*ADCK3*	Ataxia, encephalomyopathy, nephropathy	Cerebellar atrophy	CoQ10 level, genetic analysis	Coenzyme Q10
MECP2 duplication syndrome	*MECP2*	Ataxia, epilepsy, spasticity, intellectual disability, recurrent infections, hand wringing, breathing problems	Cerebellar hypoplasia, periventricular white matter hyperintensity	Genetic analysis	None
Infantile neuroaxonal dystrophy	*PLA2G6*	Developmental regression, hypotonia, nystagmus, neuropathy	Bilateral globus pallidus and dentate hypointensity, cerebellar atrophy, hyperintensity of cerebellar cortex	Genetic analysis	None
Thiamine transporter deficiency	*SLC19A3*	Ataxia, opthalmoplegia, nystagmus, seizures	Bilateral medial thalamus and periaqueductal hyperintensity, cortical-subcortical white matter lesions	Neuroimaging, genetic analysis	Thiamine
Biotinidase deficiency	*BTD*	Alopecia, skin rash, seizures, hearing loss, optic atrophy, ataxia	Myelopathy, basal ganglia hyperintensity	Serum biotinidase activity	Biotin
Pyruvate dehydrogenase deficiency	*PDHA1*	Developmental regression, seizures, acidosis, ataxia, weakness	Cortical atrophy, agenesis corpus callosum, dilated ventricles, germinolytic cysts	Plasma and CSF lactate and pyruvate, genetic analysis	Ketogenic diet, citrate, dichloroacetate
Fumarase deficiency	*FH*	GDD/ID, microcephaly, seizures, leucopenia, dysmorphic features, hypotonia	Cerebral atrophy, agenesis corpus callosum, polymicrogyria	Urine organic acid analysis, enzymatic analysis, genetic analysis	None
Galactosemia	*GALT*	Hepatomegaly, E.coli sepsis, cataracts, GDD/ID, hypotonia	White matter hyperintensity, cerebellar atrophy	Enzymatic analysis, genetic analysis	Eliminate lactose and galactose from diet

Table 6 continued

Disorder	[a]Gene(s)	[b]Distinctive characteristics	[c]Neuroimaging findings	Diagnostic tests	[d]Treatment
Creatine metabolism disorders	*AGAT, GAMT*	GDD/ID, seizures, hypotonia, behavioral changes	Globus pallidus hyperintensity, absent creatine peak on MRS	Neuroimaging, genetic analysis	Creatine, ornithine, restrict arginine
GM1 and GM2 Gangliosidoses	*GLB1, GM2A*	Hepatosplenomegaly, seizures, blindness, regression, hypotonia	Hypomyelination, basal ganglia hyperintensity	Enzymatic analysis, genetic analysis	None
Neuronal ceroid lipofuscinosis	*PPT1, CLN1, CLN2, CLN3*	Developmental regression, seizures, myoclonus, retinitis pigmentosa, ataxia	Periventricular white matter hyperintensity, cerebral and cerebellar atrophy, thalamic hypointensity	Genetic analysis	None
Late-onset GM2 gangliosidosis	*HEXA*	Developmental regression, ataxia, seizures	Pure cerebellar atrophy	Enzymatic analysis, genetic analysis	None
Angelman syndrome	*UBE3A*	GDD/ID, seizures, autism, absent speech, gait ataxia	White matter hyperintensity (periventricular, inconsistent)	Genetic analysis	None
Vanishing white matter disease	*EIF2B*	Ataxia, spasticity, seizures, encephalopathic crises after head trauma/ infections	White matter hyperintensity, cysts relatively sparing the temporal lobe and cerebellar white matter	Neuroimaging, genetic analysis	None
Hypomyelination with congenital cataract	*FAM126A*	Cataracts, GDD, spasticity, ataxia	Hypomyelination	Genetic analysis	None
L-2-hydroxyglutaric aciduria	*L2HGDH*	Ataxia, microcephaly, seizures, regression	Subcortical white matter hyperintensity sparing deep white matter, dentate nuclei hyperintensity	Urinary organic acids analysis, genetic analysis	None
Rhombencephalosynapsis	None	Ataxia, head nodding, often intellectual disability	Agenesis cerebellar vermis, fused cerebellar hemispheres, hydrocephalus	Neuroimaging	
4H syndrome	*POLR3A*	Ataxia, delayed dentition, growth failure	Hypomyelination, cerebellar atrophy	Genetic analysis	None
Infantile sialic acid storage disease (Salla disease)	*SLC17A5*	GDD/ID, seizures, cardiomegaly, hepatomegaly, ataxia, hypotonia, transient nystagmus	Hypomyelination, cerebellar atrophy	Urine sialic acid analysis, genetic analysis	None
Metachromatic leukodystrophy	*ARSA*	Developmental regression, seizures, ataxia, neuropathy	Demyelination in supratentorial deep white matter with sparing of U-fibers, tigroid pattern	Enzymatic analysis, genetic analysis	None
Peroxisome biogenesis disorders	*PEX*	GDD/ID, distinct facial features, hepatic disease, hearing loss, seizures, hypotonia	White matter hyperintensity (supratentorial and cerebellar), polymicrogyria, germinolytic cysts	VLCFA analysis, genetic analysis	None
Canavan disease	*ASPA*	Hypotonia, developmental regression, macrocephaly	Demyelination (subcortical earlier than deep white matter), thalamic hyperintensity, NAA peak on MRS	Urine NAA analysis, enzymatic analysis, genetic analysis	None

Table 6 continued

Disorder	[a]Gene(s)	[b]Distinctive characteristics	[c]Neuroimaging findings	Diagnostic tests	[d]Treatment
Merosin-deficient muscular dystrophy	*LAMA2*	Hypotonia, profound weakness, increased creatine kinase	Diffuse white matter hyperintensity	Muscle biopsy, genetic analysis	None
Abetalipoproteinemia	*MTTP*	Fat soluble vitamin deficiency, ataxia, sensory neuropathy, retinitis pigmentosa, steatorrhea	None	Serum cholesterol, genetic analysis	Vitamin E; triglyceride restriction
Phenylketonuria	*PAH*	GDD/ID, seizures, autism, hypotonia	Parieto-occipital white matter hyperintensity	Newborn screening, plasma phenylalanine level, genetic analysis	Low phenylalanine diet; BH_4
Methylmalonic Acidemia	*MMA*	GDD/ID, hyperammonemia, seizures, hypotonia	Globus pallidus hyperintesity	Urinary organic acids or acylcarnitines analysis, enzymatic analysis, genetic analysis	Low protein diet; carnitine and cobalamin
Gaucher disease, Type II and III	*GBA*	Hepatosplenomegaly, eye movement disorders, GDD/ID, myoclonic seizures, ataxia	None	Enzymatic analysis, genetic analysis	IV glucocerebrosidase enzyme replacement
Congenital disorders of glycosylation	*PMM2*	GDD/ID, multiorgan involvement, ataxia, hypotonia	Stroke, white matter cysts, cerebellar hypoplasia with superimposed atrophy, pontine hypoplasia	Transferrin isoform analysis, genetic analysis	None
Duchenne muscular dystrophy	*DMD*	Weakness, pseudohypertrophy, cognitive delay, cardiomyopathy	None	CK, Genetic analysis	None
Rett and Rett-like syndromes	*MECP2, CDKL5, FOXG1*	Developmental regression, seizures, hand wringing, microcephaly, apnea, hyperpnea, gait dyspraxia	Cerebral atrophy with predominance in parietal gray matter	Genetic analysis	None

[a] Gene(s) most commonly associated with disease

[b] Salient disease characteristics. GDD/ID: Global developmental disability/Intellectual disability

[c] Magnetic resonance imaging findings that may assist in characterization of disease. Intensity is discussed with respect to T2-weighted image sequences

[d] Potentially disease modifying or curative treatment, not including supportive therapy

Khankhanian et al. BMC Medical Genetics 2013, 14:126
http://www.biomedcentral.com/1471-2350/14/126

BMC Medical Genetics

RESEARCH ARTICLE Open Access

Sequencing of the IL6 gene in a case–control study of cerebral palsy in children

Pouya Khankhanian[1*], Sergio E Baranzini[1], Britt A Johnson[1], Lohith Madireddy[1], Dorothee Nickles[1], Lisa A Croen[2] and Yvonne W Wu[1,3*]

Abstract

Background: Cerebral palsy (CP) is a group of nonprogressive disorders of movement and posture caused by abnormal development of, or damage to, motor control centers of the brain. A single nucleotide polymorphism (SNP), rs1800795, in the promoter region of the *interleukin-6* (IL6) gene has been implicated in the pathogenesis of CP by mediating IL-6 protein levels in amniotic fluid and cord plasma and within brain lesions. This SNP has been associated with other neurological, vascular, and malignant processes as well, often as part of a haplotype block.

Methods: To refine the regional genetic association with CP, we sequenced (Sanger) the IL6 gene and part of the promoter region in 250 infants with CP and 305 controls.

Results: We identified a haplotype of 7 SNPs that includes rs1800795. In a recessive model of inheritance, the variant haplotype conferred greater risk (OR = 4.3, CI = [2.0-10.1], p = 0.00007) than did the lone variant at rs1800795 (OR = 2.5, CI = [1.4-4.6], p = 0.002). The risk haplotype contains one SNP (rs2069845, CI = [1.2-4.3], OR = 2.3, p = 0.009) that disrupts a methylation site.

Conclusions: The risk haplotype identified in this study overlaps with previously identified haplotypes that include additional promoter SNPs. A risk haplotype at the IL6 gene likely confers risk to CP, and perhaps other diseases, via a multi-factorial mechanism.

Keywords: Cerebral palsy, Sanger sequencing, IL-6, Interleukin-6, Haplotype

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BRAIN
A JOURNAL OF NEUROLOGY

De novo point mutations in patients diagnosed with ataxic cerebral palsy

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Dedicated to the memory of Dr John Tolmie who tragically died during the preparation of this manuscript.

Cerebral palsy is a sporadic disorder with multiple likely aetiologies, but frequently considered to be caused by birth asphyxia. Genetic investigations are rarely performed in patients with cerebral palsy and there is little proven evidence of genetic causes. As part of a large project investigating children with ataxia, we identified four patients in our cohort with a diagnosis of ataxic cerebral palsy. They were investigated using either targeted next generation sequencing or trio-based exome sequencing and were found to have mutations in three different genes, *KCNC3*, *ITPR1* and *SPTBN2*. All the mutations were *de novo* and associated with increased paternal age. The mutations were shown to be pathogenic using a combination of bioinformatics analysis and *in vitro* model systems. This work is the first to report that the ataxic subtype of cerebral palsy can be caused by *de novo* dominant point mutations, which explains the sporadic nature of these cases. We conclude that at least some subtypes of cerebral palsy may be caused by *de novo* genetic mutations and patients with a clinical diagnosis of cerebral palsy should be genetically investigated before causation is ascribed to perinatal asphyxia or other aetiologies.

Molecular Psychiatry (2015) 20, 176–182

www.nature.com/mp

IMMEDIATE COMMUNICATION

Whole-exome sequencing points to considerable genetic heterogeneity of cerebral palsy

G McMichael[1], MN Bainbridge[2], E Haan[3,4], M Corbett[1,4], A Gardner[1,4], S Thompson[4,5], BWM van Bon[3,6], CL van Eyk[1], J Broadbent[1], C Reynolds[1], ME O'Callaghan[1], LS Nguyen[4], DL Adelson[7], R Russo[8], S Jhangiani[2], H Doddapaneni[2], DM Muzny[2], RA Gibbs[2], J Gecz[1,4,9,10] and AH MacLennan[1,9,10]

Cerebral palsy (CP) is a common, clinically heterogeneous group of disorders affecting movement and posture. Its prevalence has changed little in 50 years and the causes remain largely unknown. The genetic contribution to CP causation has been predicted to be ~2%. We performed whole-exome sequencing of 183 cases with CP including both parents (98 cases) or one parent (67 cases) and 18 singleton cases (no parental DNA). We identified and validated 61 *de novo* protein-altering variants in 43 out of 98 (44%) case-parent trios. Initial prioritization of variants for causality was by mutation type, whether they were known or predicted to be deleterious and whether they occurred in known disease genes whose clinical spectrum overlaps CP. Further, prioritization used two multidimensional frameworks—the Residual Variation Intolerance Score and the Combined Annotation-dependent Depletion score. Ten *de novo* mutations in three previously identified disease genes (*TUBA1A* ($n=2$), *SCN8A* ($n=1$) and *KDM5C* ($n=1$)) and in six novel candidate CP genes (*AGAP1*, *JHDM1D*, *MAST1*, *NAA35*, *RFX2* and *WIPI2*) were predicted to be potentially pathogenic for CP. In addition, we identified four predicted pathogenic, hemizygous variants on chromosome X in two known disease genes, *L1CAM* and *PAK3*, and in two novel candidate CP genes, *CD99L2* and *TENM1*. In total, 14% of CP cases, by strict criteria, had a potentially disease-causing gene variant. Half were in novel genes. The genetic heterogeneity highlights the complexity of the genetic contribution to CP. Function and pathway studies are required to establish the causative role of these putative pathogenic CP genes.

Molecular Psychiatry (2015) **20,** 176–182; doi:10.1038/mp.2014.189; published online 10 February 2015

Genetic insights into the causes and classification of the cerebral palsies

Andres Moreno-De-Luca, David H Ledbetter, Christa L Martin

Cerebral palsy—the most common physical disability of childhood—is a clinical diagnosis encompassing a heterogeneous group of neurodevelopmental disorders that cause impairments of movement and posture that persist throughout life. Despite being commonly attributed to a range of environmental factors, particularly birth asphyxia, the specific cause of cerebral palsy remains unknown in most individuals. A growing body of evidence suggests that cerebral palsy is probably caused by multiple genetic factors, similar to other neurodevelopmental disorders such as autism and intellectual disability. Recent advances in next-generation sequencing technologies have made possible rapid and cost-effective sequencing of the entire human genome. Novel cerebral palsy genes will probably be identified as more researchers and clinicians use this approach to study individuals with undiagnosed neurological disorders. As our knowledge of the underlying pathophysiological mechanisms of cerebral palsy increases, so will the possibility of developing genomically guided therapeutic interventions.

Lancet Neurol 2012; 11: 283–92
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DOI:10.1016/S1474-4422(11)70287-3

This publication has been corrected. The corrected version first appeared at thelancet.com/neurology on February 15, 2012

See Errata page 208

	Name	OMIM ID	Inheritance	Reference
GAD1	Glutamate decarboxylase 1	603513	AR	Lynex et al[59]
KANK1	KN motif and ankyrin repeat domains 1	612900	AD	Lerer et al[60]
AP4M1	Adaptor-related protein complex 4, μ1 subunit	612936	AR	Verkerk et al[61]
AP4E1	Adaptor-related protein complex 4, ε1 subunit	613744	AR	Moreno-De-Luca et al[62]
AP4B1	Adaptor-related protein complex 4, β1 subunit	614066	AR	Abou Jamra et al[63]
AP4S1	Adaptor-related protein complex 4, σ1 subunit	614067	AR	Abou Jamra et al[63]

OMIM=Online Mendelian Inheritance in Man. AR=autosomal recessive. AD=autosomal dominant.

Table 1: Genes associated with cerebral palsy

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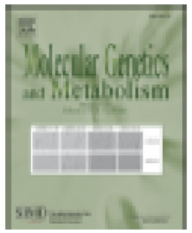

Review article

Clinical and biochemical footprints of inherited metabolic disease. V. Cerebral palsy phenotypes

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ABSTRACT

Cerebral palsy is the most common physical disability of childhood describing a heterogeneous group of neurodevelopmental disorders that cause activity limitation, but often are accompanied by disturbances of sensation, perception, cognition, communication and behavior, or by epilepsy. Inborn errors of metabolism have been reported in the literature as presenting with features of cerebral palsy. We reviewed and updated the list of metabolic disorders known to be associated with symptoms suggestive of cerebral palsy and found more than 150 relevant IEMs. This represents the fifth of a series of articles attempting to create and maintain a comprehensive list of clinical and metabolic differential diagnosis according to system involvement.

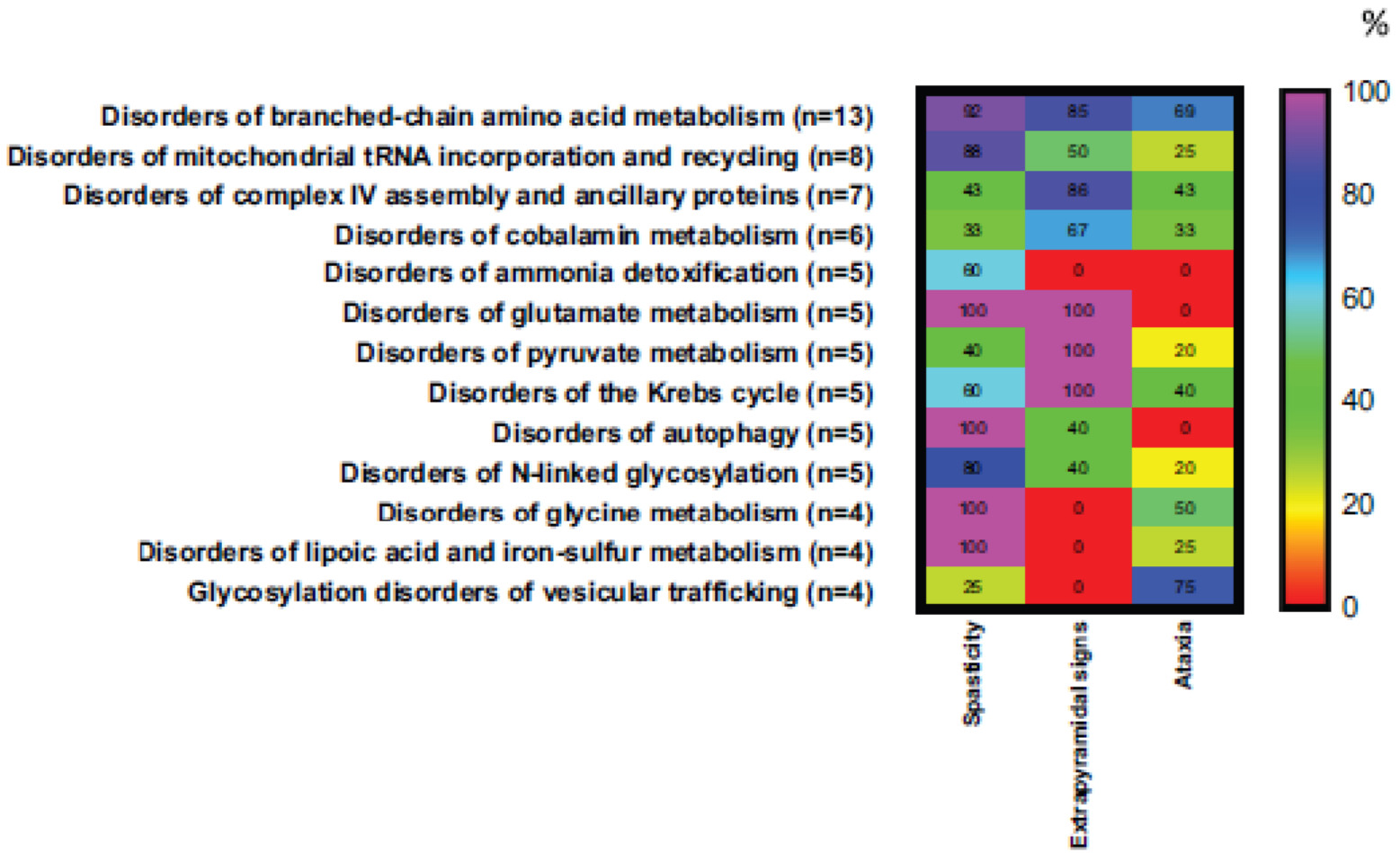

Fig. 1. Occurrence (%) of spasticity, extrapyramidal signs or ataxia in a combination with developmental delay or impairment or regression in 13 categories of IEMs. The percentages for neurological involvement were calculated using as the denominator the total number of IEMs in each category presenting with spasticity, extrapyramidal signs or ataxia. Heat scale ranges from red (0%) for diseases with no particular symptoms reported to violet (100%) for diseases with particular symptoms occurring with highly frequency. For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Anales de Pediatría 95 (2021) 276.e1–276.e11

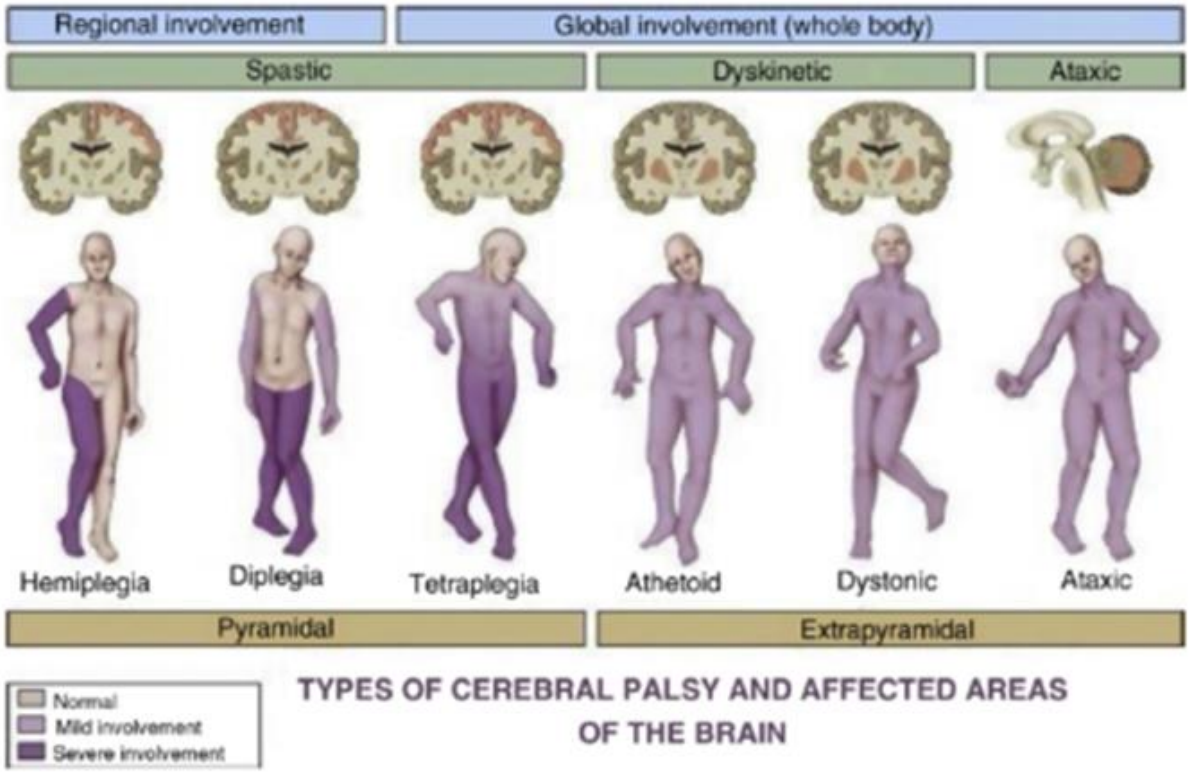

Figure 1 Types of cerebral palsy and affected areas of the brain.

2010 Foundation Acta Pædiatrica/*Acta Pædiatrica* 2010 **99**, pp. 1337–1343

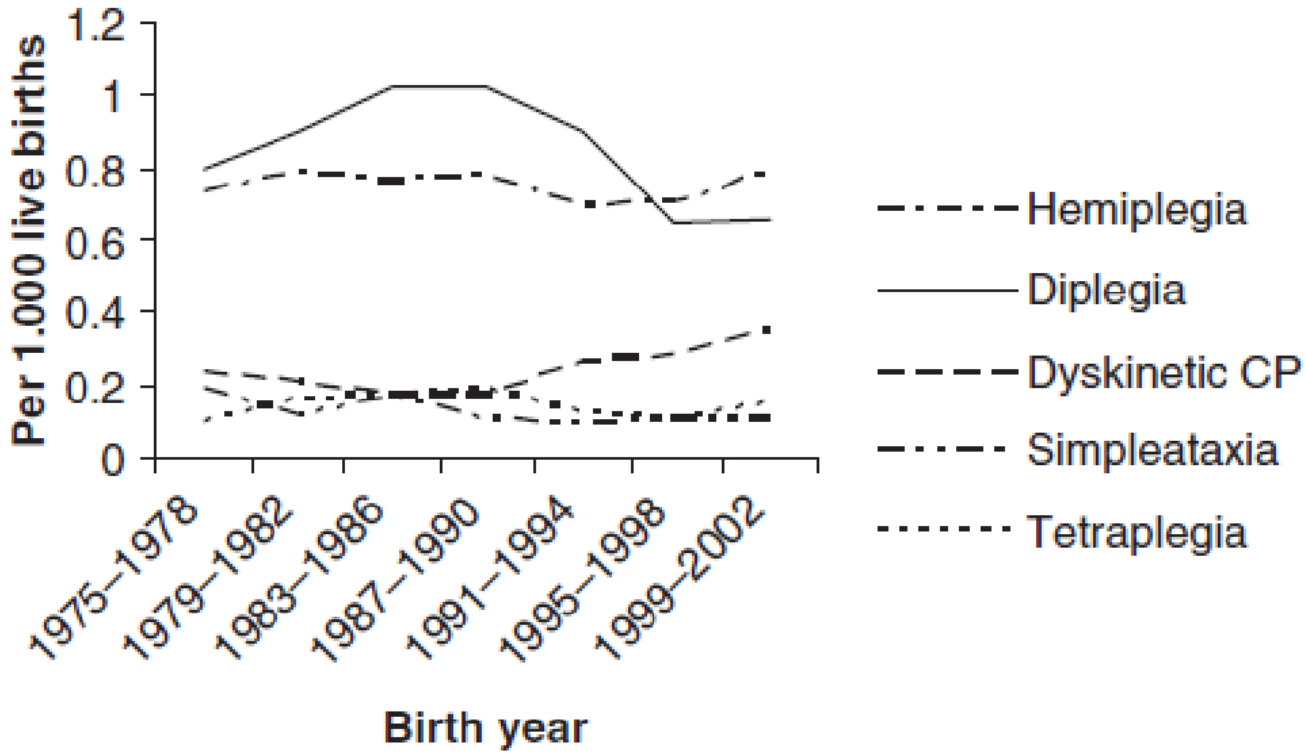

Figure 4 Prevalence of CP by CP type, according to Hagberg's classification, 1975–2002.

Table 1 – Geographical classification of cerebral palsy.

Major types	Description
Monoplegia	• One extremity involved, usually lower
Hemiplegia (30%)	• Both extremities on same side involved • Usually upper extremity involved more than lower extremity
Paraplegia	• Both lower extremities equally involved
Diplegia (50%)	• Lower extremities more involved than upper extremities • Fine-motor/sensory abnormalities in upper extremity
Quadriplegia	• All extremities involved equally • Normal head/neck control
Double hemiplegia	• All extremities involved, upper more than lower
Total body	• All extremities severely involved • No head/neck control

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Table 2 – Physiological classification of cerebral palsy.

Major types	Description
Spastic (80%)	• Velocity-dependent increase in muscle tone with passive stretch • Joint contractures are common
Athetoid	• Dyskinetic, purposeless movements • Joint contractures are uncommon • Dystonia or hypotonia can be associated
Choreiform	• Continual purposeless movements
Rigid	• Hypertonicity occurs in the absence of hyperreflexia, spasticity and clonus • "Cogwheel" or "lead pipe" muscle stiffness
Ataxic	• Disturbance of coordinated movement, most commonly walking • Normal head/neck control
Hypotonic	• Low muscle tone and normal deep tendon reflexes
Mixed	• Features of more than one type • No head/neck control

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Table 3: SCPE classification of cerebral palsy [2, 13].

Type of CP	Description
Spastic	Presents with hypertonicity and hyperreflexia May be unilateral or bilateral
Dyskinetic	Presents with involuntary, uncontrolled, repetitive, and sometimes stereotype movements with altered muscle tone Abnormal posture with hypertonicity is termed dystonic A quick, uncontrolled, and twisting movement with hypotonia is called choreoathetosis
Ataxic	In coordination with a decreased muscle tone

Tratto da: *Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Surveillance of Cerebral Palsy in Europe (SCPE),* Dev Med Child Neurol. 2000 Dec;42(12):816-24.

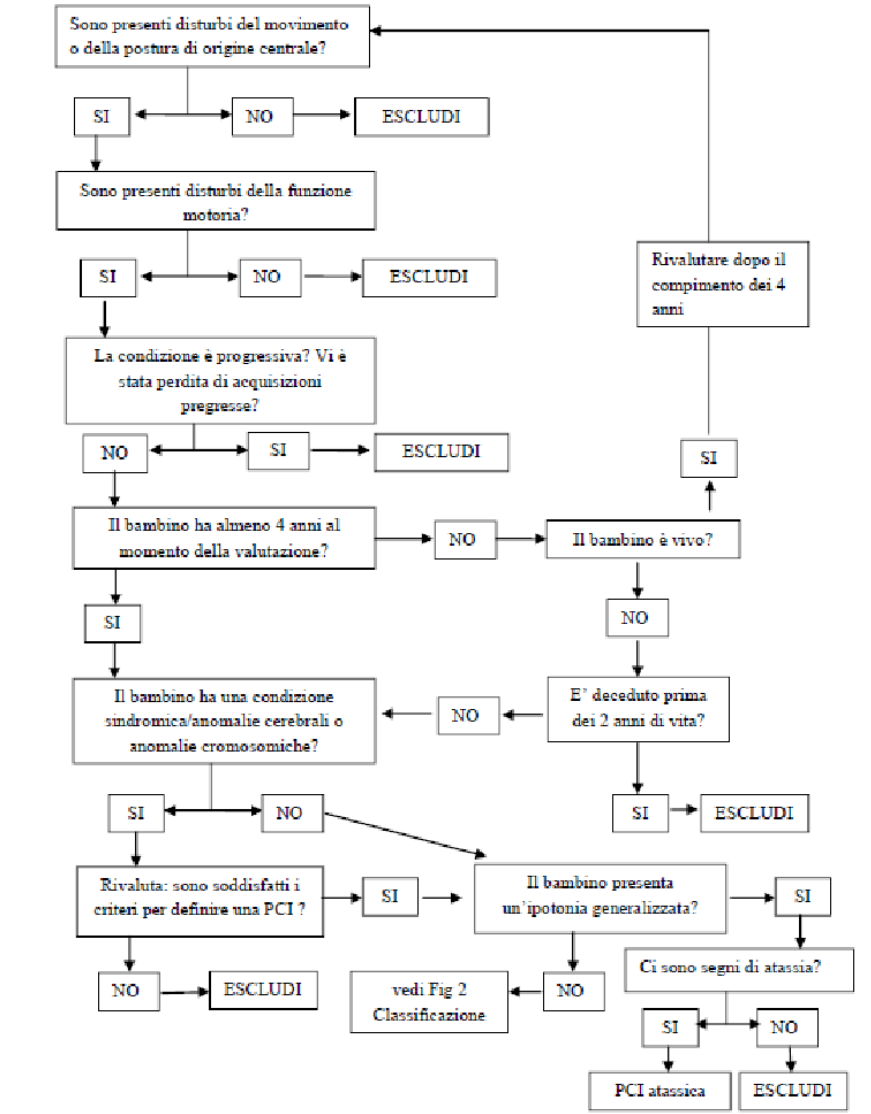


Figura 1. Flow chart utilizzata dal network di lavoro denominato *Surveillance of cerebral palsy in Europe (SCPE)* per identificare i casi di PCI da includere e/o escludere dal registro europeo.

Tratto da: *Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Surveillance of Cerebral Palsy in Europe (SCPE),* Dev Med Child Neurol. 2000 Dec;42(12):816-24.

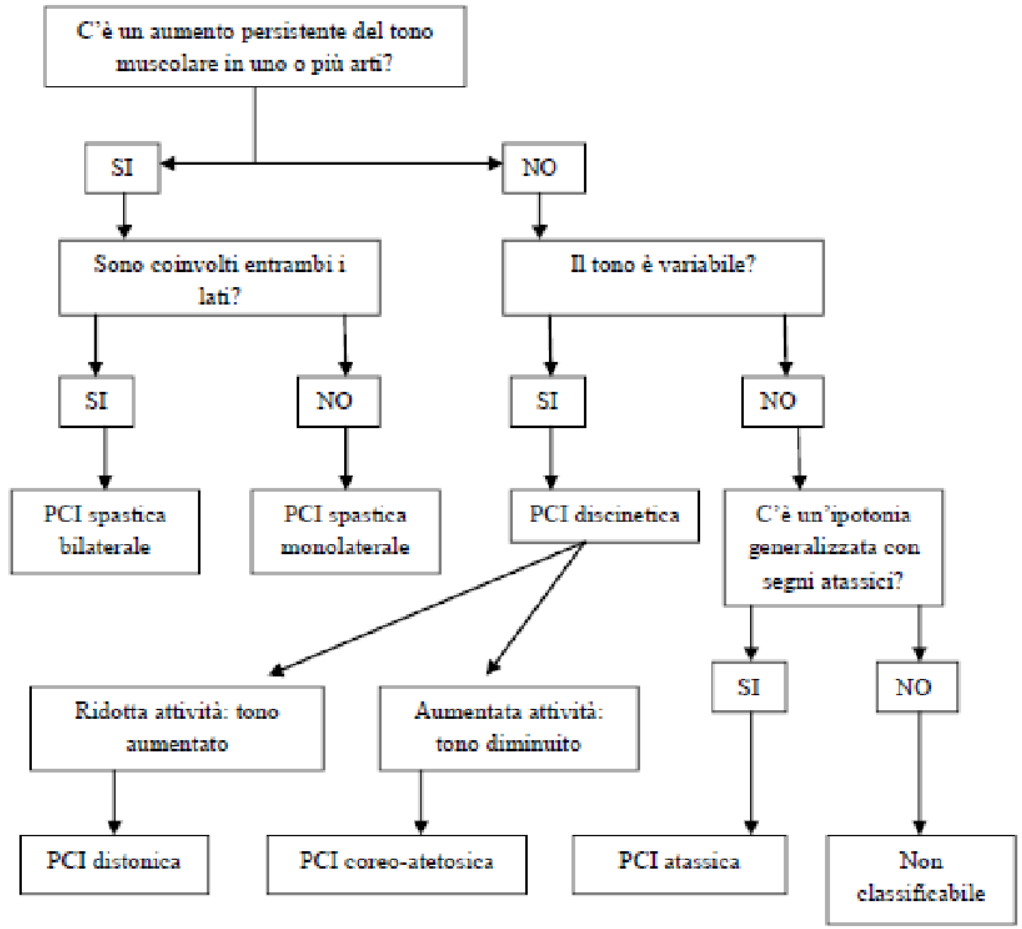
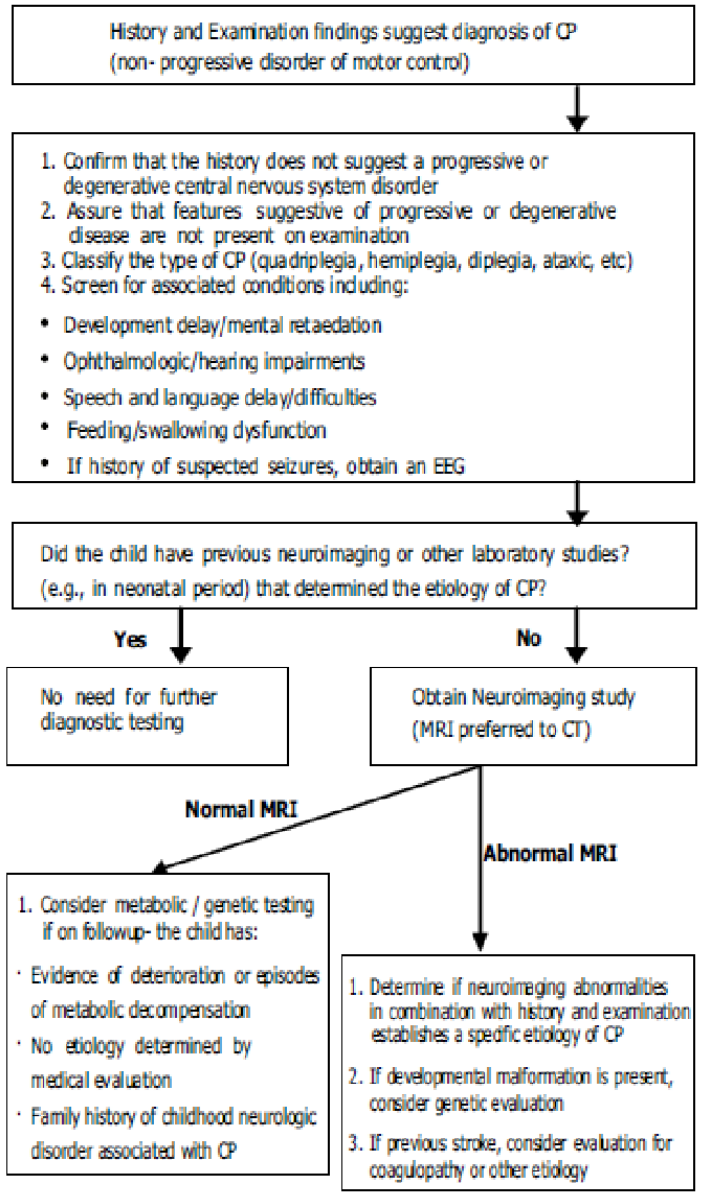


Figura 2. Flow chart utilizzata dal network di lavoro denominato Surveillance of cerebral palsy in Europe (SCPE) per classificare i casi di PCI nei diversi sottotipi.

An algorithm for the evaluation of the child with CP according to American Academy of Neurology (AAN) practice parameter on CP (2004)



Ashwal S, Russman BS, et al. Practice Parameter: Diagnostic Assessment of the Child with Cerebral Palsy. Report of the Quality Standard Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2004; 62(6):851-863.

Tratto da: *Practice Parameter: Diagnostic assessment of the child with cerebral palsy : Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society.* Neurology 2004;62;851.

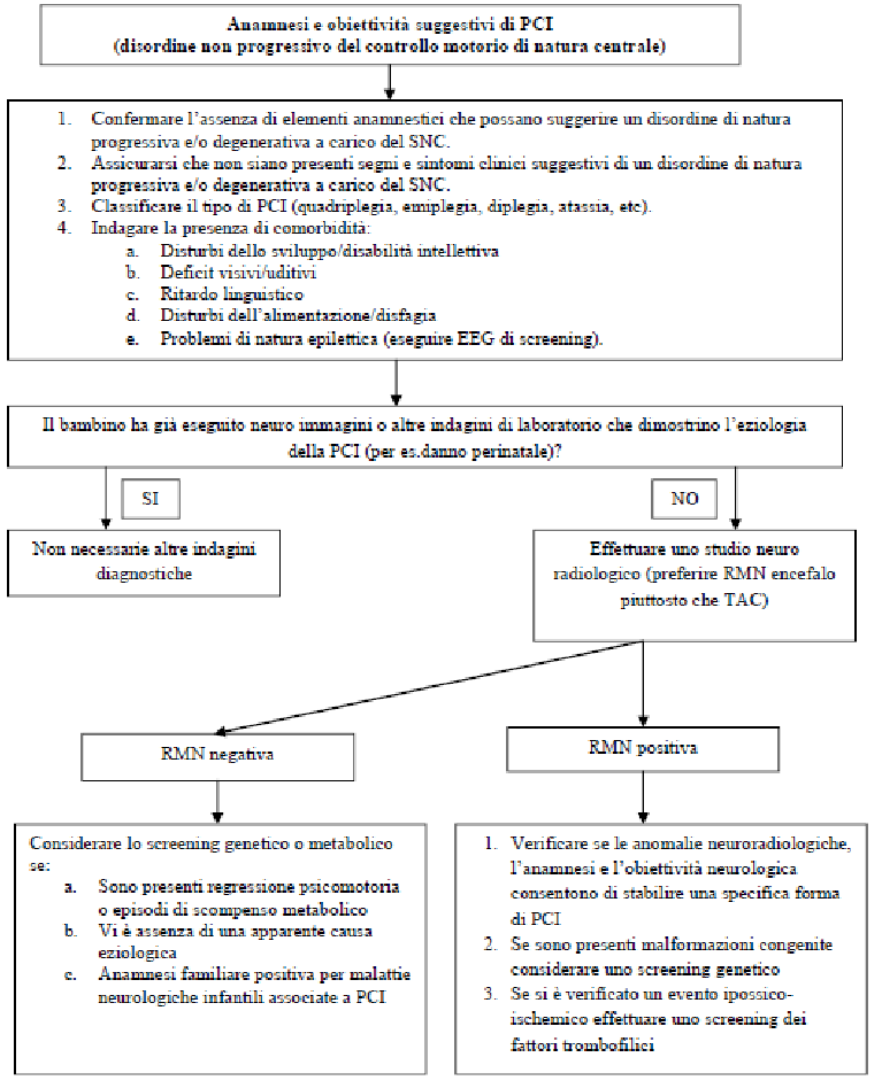


Figura 3: Flow chart sviluppata dall'American Academy of Neurology per l'inquadramento clinico e eziologico del bambino con sospetta PCI .

DIAGNOSIS OF CEREBRAL PALSY

The diagnosis of CP relies on a combination of neurologic assessment, neuroimaging findings, and recognition of clinical risk factors. Diagnosis is thus often complicated and delayed, and typically occurs at the age of 1 to 2 years or beyond [3]. In recent years, earlier and accurate diagnosis of CP has become possible and highly desirable, because it allows earlier initiation of therapies that may improve long-term outcomes during the period of rapid brain growth and neuroplasticity. Moreover, contrary to concerns that attempts at earlier diagnosis may lead to false-positive screens and create unnecessary parental stress, population studies have shown that parents generally prefer to know if their child has CP or is at high risk for CP sooner rather than later, so that they can start therapies that may optimize their child's development [4,5].

A recent review by a multidisciplinary, international group of CP experts focused on the following tools with the best predictive validity for detection of CP before 5 months of age:

Neonatal magnetic resonance imaging (MRI) (86%–89% sensitivity),

the Prechtl Qualitative Assessment of General Movements (GMA) (98% sensitivity),

Hammersmith Infant Neurologic Examination (HINE) (90% sensitivity)

Movimenti generalizzati (GM)

Tab. 1.5. *Principali caratteristiche dei GM nel bambino normale correlate all'età* (modificata da [19, 24]).

Tipo di GM	*Periodo di vita postnatale*	*Caratteristiche*
GM del pretermine	28ª → 36ª-38ª settimana	Movimenti assai variabili: scatti della pelvi e movimenti del tronco
Writhing GM	36ª-38ª → 46ª-52ª settimana	Ai movimenti variabili si aggiungono movimenti più energici (writhing). In rapporto ai GM del pretermine i GM writhing sembrano essere più lenti con minore partecipazione della pelvi e del tronco
Fidgety GM	46ª-52ª → 54ª-58ª settimana	La motilità spontanea di base qui consiste in un flusso continuo di piccoli ed eleganti movimenti irregolari di tutto il corpo (il capo, il tronco e gli arti partecipano insieme al movimento che viene definita "danza fidgety"). A questi movimenti più lenti si sovrappongono movimenti più ampi e veloci

• *complessità del movimento*: il bambino deve produrre attivamente movimenti con frequenti cambiamenti della direzione delle parti del corpo coinvolte nel movimento. Vi devono essere variazioni nella combinazione di movimenti di flessione/estensione, abduzione/adduzione ed endorotazione/extrarotazione delle articolazioni che partecipano al movimento

• *variabilità del movimento*: il bambino deve produrre nel tempo pattern di movimento sempre nuovi

• *fluidità* movimenti variabili da lenti a medi e occasionali *interruzioni* da parte di movimenti veloci, ampi ed ellittici dei muscoli estensori delle braccia.

SWIPPING MOVEMENTS

bruschi e rapidi movimenti degli arti superiori verso l'alto e all'indietro, con inizio molto rapido e fine più graduale

SWATTING MOVEMENTS

movimenti rapidi e potenti degli arti superiori verso il basso e in avanti, con inizio e fine bruschi, spesso riuniti in *bursts*.

dopo le 8 settimane la loro frequenza è correlata al "temperamento" del bambino.

Effetto degli stati comportamentali sui GM normali.

Stato comportamentale	*Complessità e variazione*	*Fluidità*
Stadio 2, sonno attivo o sonno REM	Normali	Ridotta
Stadio 4, veglia attiva	Normali	Normale
Stadio 5, pianto	Ridotte	Ridotta
Fase di suzione (non a fini nutritivi)	Ridotte	Normale

Classificazione della qualità dei GM

Classificazione	*Complessità*	*Variazione*	*Fluidità*
GM normali-ottimali	+++	+++	+
GM normali-subottimali	++	++	–
GM lievemente anormali	+	+	–
GM decisamente anormali	–	–	–

I **GM** sono **patologici**

repertorio GM *povero* (*scarso)*

GM *sincronizzati-limitati*

GM *caotici*

Fidgety movements (FM)

I FM sono movimenti presenti dalla 6_a- 12_a settimana di vita sino al 5° mese di vita dopo la nascita. Nel lattante normale sono caratterizzati da movimenti agitati e irrequieti (*fidgety*)

ampiezza (generalmente ridotta)
velocità (generalmente media)
accelerazioni (variabili in tutte le direzioni)

I FM sono **patologici** quando i FM sono:
- *assenti*: ciò accade anche in presenza di altri movimenti;
- *esagerati*: cioè si hanno movimenti di ampiezza, velocità e accelerazione ampia, esagerata.

HAMMERSMITH INFANT NEUROLOGICAL EXAMINATION (v 07.07.17)

Name **Date of birth**

Gestational age **Date of examination**

Chronological age / Corrected age **Head circumference**

SUMMARY OF EXAMINATION
Global score (max 78)
Number of asymmetries
Behavioural score (not part of the optimality score)

Cranial nerve function	**score**	**(max 15)**
Posture	**score**	**(max 18)**
Movements	**score**	**(max 6)**
Tone	**score**	**(max 24)**
Reflexes and reactions	**score**	**(max 15)**

COMMENTS

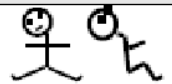
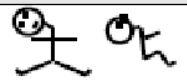
(Throughout the exam, if a response is not optimal but not poor enough to score 1, give a score of 2)

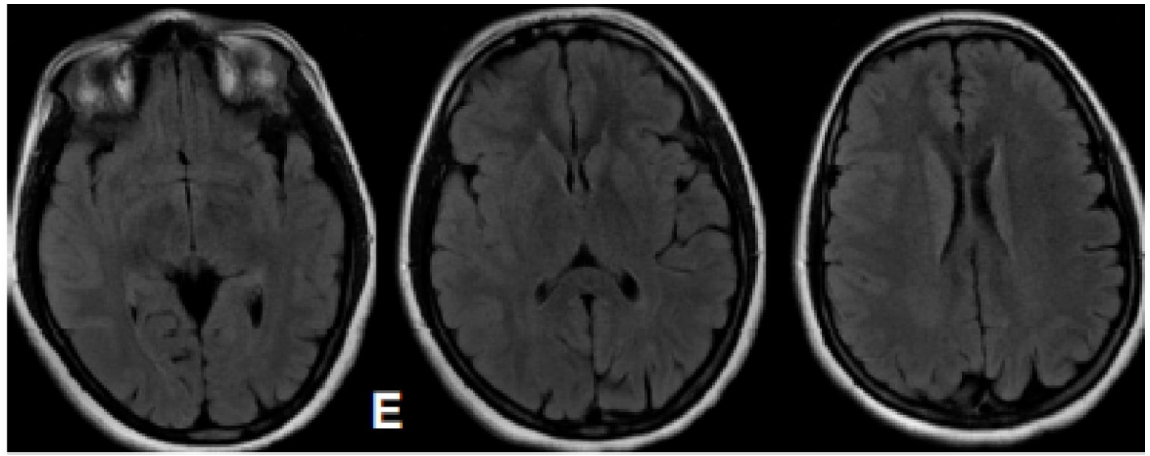
NEUROLOGICAL EXAMINATION

ASSESSMENT OF CRANIAL NERVE FUNCTION

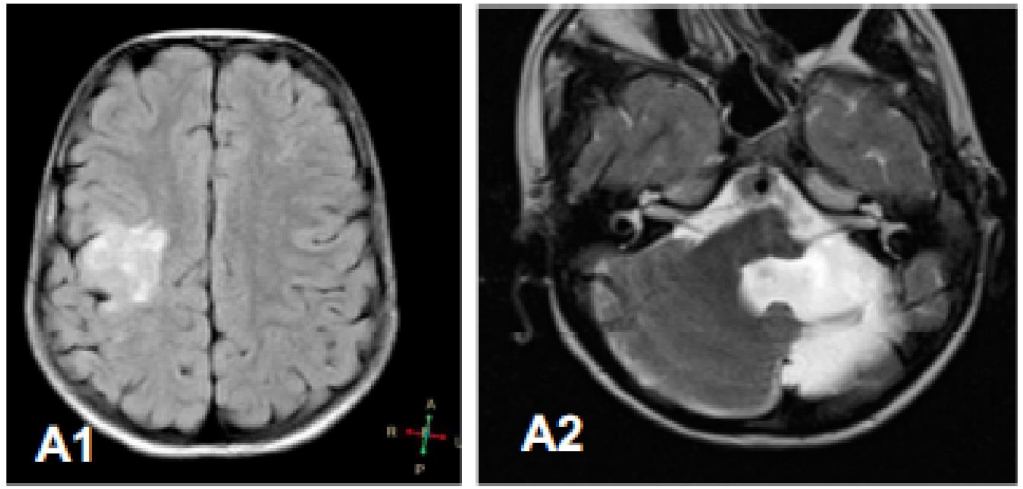
	score 3	2	score 1	score 0	score	Asymmetry / Comments
Facial appearance (at rest and when crying or stimulated)	Smiles or reacts to stimuli by closing eyes and grimacing		Closes eyes but not tightly, poor facial expression	Expressionless, does not react to stimuli		
Eye movements	Normal conjugate eye movements		**Intermittent** Deviation of eyes or abnormal movements	**Continuous** Deviation of eyes or abnormal movements		
Visual response Test ability to follow a black/white target	Follows the target in a complete arc		Follows target in an incomplete or asymmetrical arc	Does not follow the target		
Auditory response Test the response to a rattle	Reacts to stimuli from both sides		Doubtful reaction to stimuli or asymmetry of response	No response		
Sucking/swallowing Watch infant suck on breast or bottle. If older, ask about feeding, assoc. cough, excessive dribbling	Good suck and swallowing		Poor suck and/or swallow	No sucking reflex, no swallowing		

ASSESSMENT OF POSTURE (note any asymmetries)

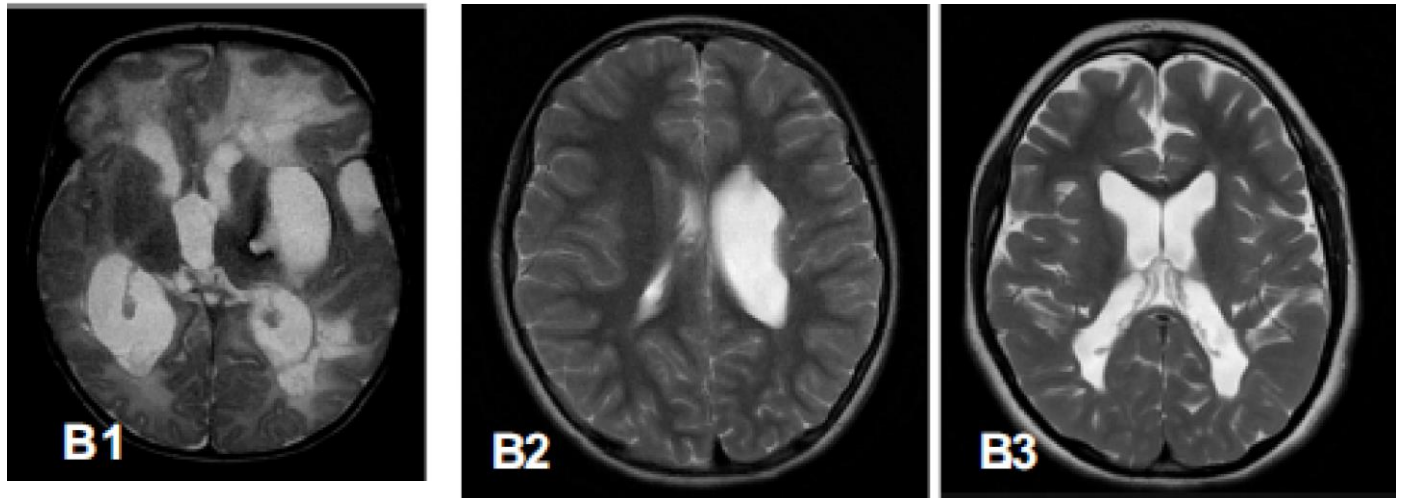
	score 3	score 2	score 1	score 0	sc	Asymmetry / comments
Head in sitting	 Straight; in midline		 Slightly to side *or* backward *or* forward	 Markedly to side *or* backward *or* forward		
Trunk in sitting	 Straight		 Slightly curved or bent to side	 Very rounded rocketing back bent sideway		
Arms at rest	In a neutral position, central straight or slightly bent		**Slight** internal rotation *or* external rotation **Intermittent** dystonic posture	**Marked** internal rotation *or* external rotation *or* dystonic posture hemiplegic posture		
Hands	Hands open		**Intermittent** adducted thumb or fisting	**Persistent** adducted thumb or fisting		
Legs in sitting in supine and in standing	Able to sit with a straight back and legs straight or slightly bent (long sitting)  Legs in neutral position straight *or* slightly bent	**Slight** internal rotation or external rotation	Sit with straight back but knees bent at 15-20 °  Internal rotation or external rotation at the hips	Unable to sit straight unless knees markedly bent (no long sitting)  **Marked** internal rotation *or* external rotation *or* fixed extension or flexion or contractures at hips and knees		
Feet in supine and in standing	Central in neutral position Toes straight midway between flexion and extension		**Slight** internal rotation *or* external rotation **Intermittent** Tendency to stand on tiptoes or toes up or curling under	**Marked** internal rotation *or* external rotation at the ankle **Persistent** Tendency to stand on tiptoes or toes up or curling under		



RM nella norma

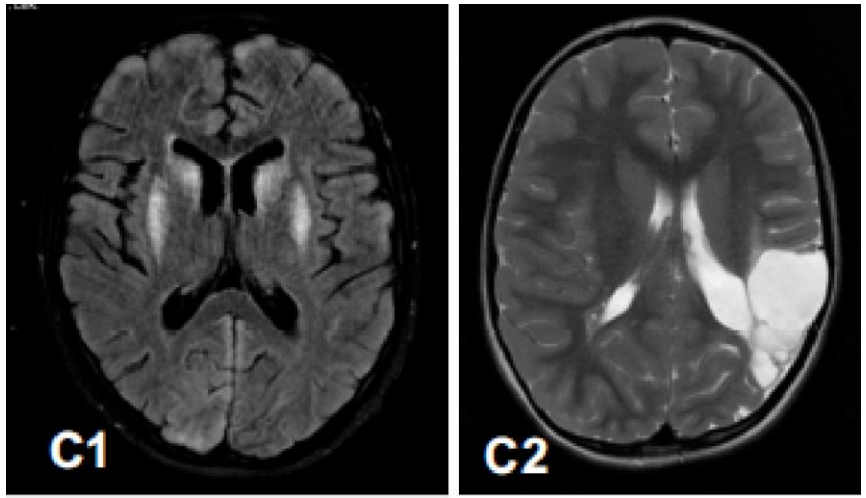


MALFORMAZIONI CORTICALI

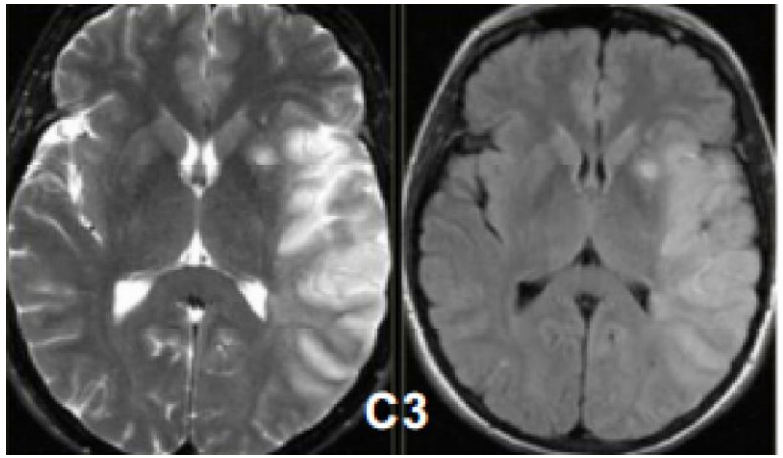


PVL

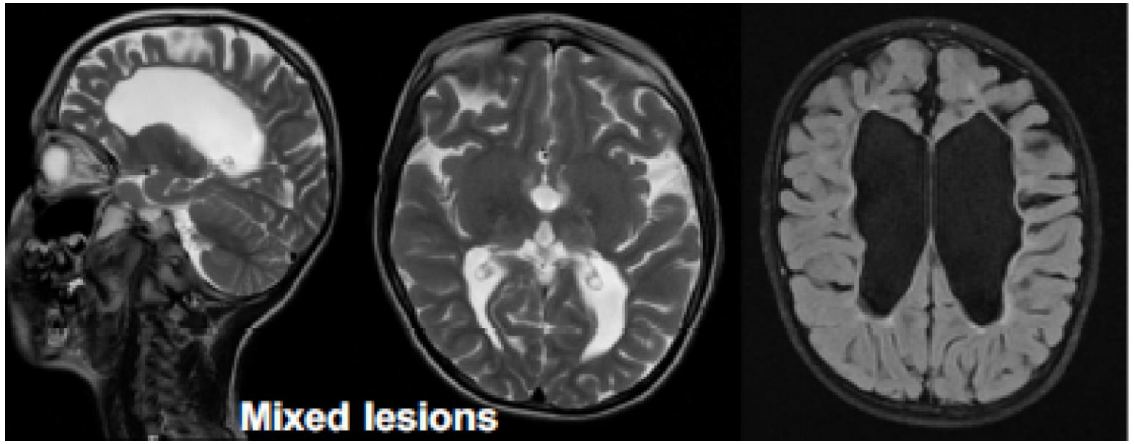
SEQUELE IVH e PERIVENTRICOLARI



LESIONI TALAMO e GANGLI



Infarto Arterioso


Mixed lesions

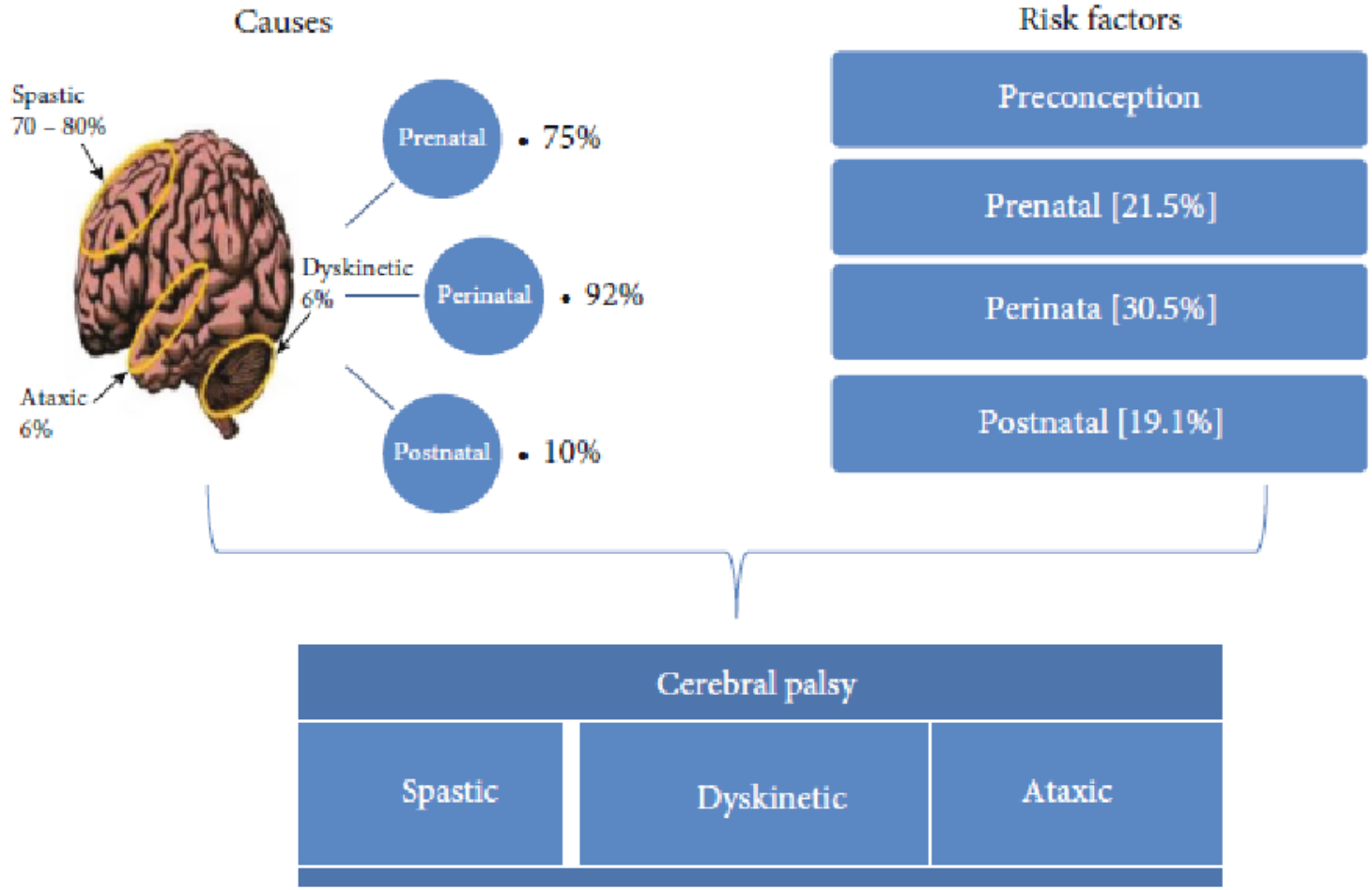


FIGURE 3: Events leading to cerebral palsy [2, 8, 11–13, 15].

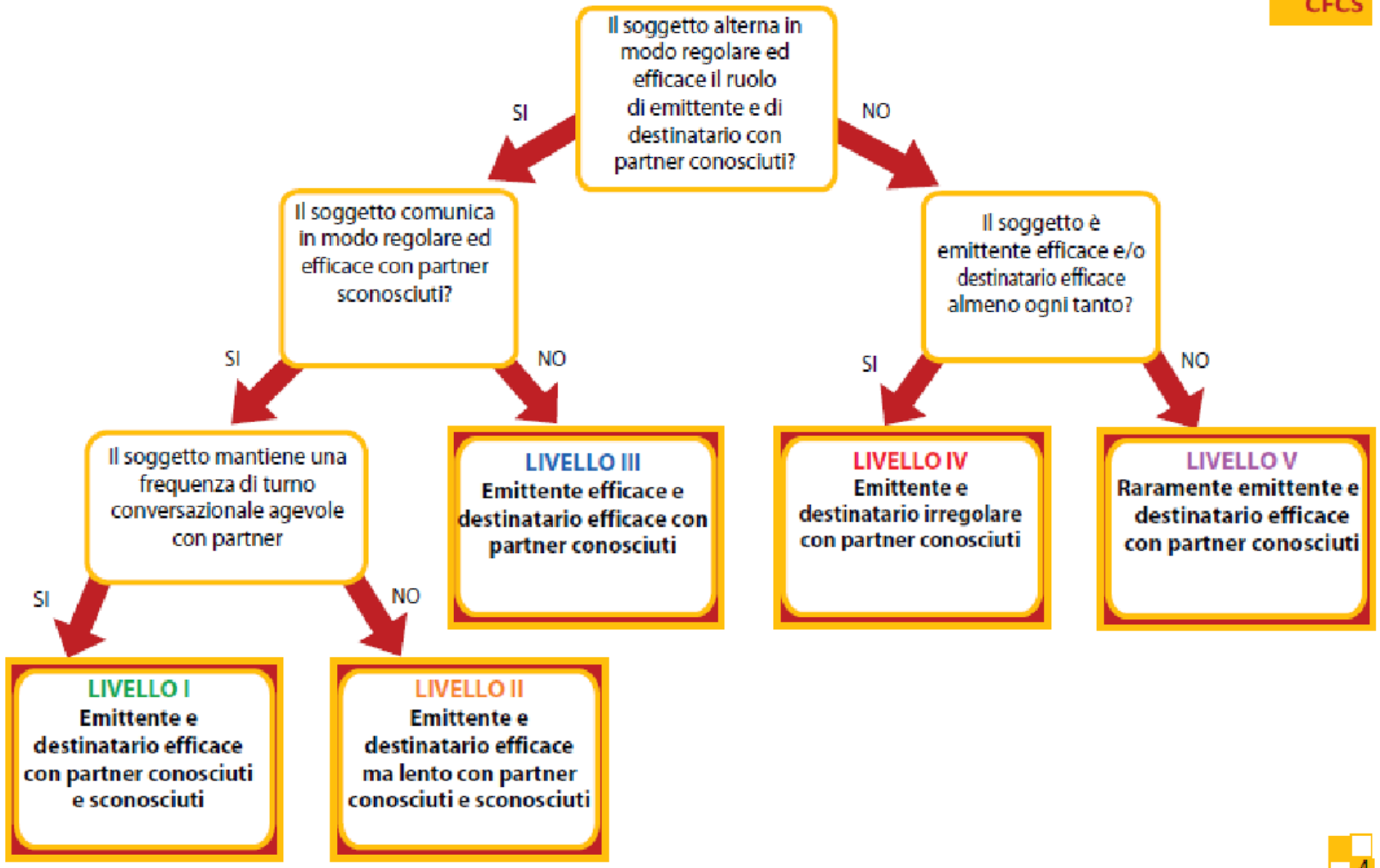
Table 1 Scales used to assess the level of independence and functioning in CP.

	GMFCS	MACS	CFCS
I	Walks without assistance, limitations in more advanced motor skills	Handles objects easily and successfully	Effective sender and receiver with unfamiliar and familiar partners
II	Walks with restrictions	Handles most objects but with somewhat reduced quality or speed of achievement	Effective but slower paced sender and/or receiver with unfamiliar and familiar partners
III	Walks with handheld assistive mobility devices	Handles objects with difficulty; needs help to prepare or modify activities	Effective sender and receiver with familiar partners
IV	Self-mobility with limitations, can be achieved using powered mobility	Handles a limited selection of easily managed objects in adapted situations	Sometimes effective sender and receiver with familiar partners
V	Patient needs to be transported by another person in a wheelchair	Does not handle objects and has severely limited ability to perform even simple actions	Seldom effective sender and receiver even with familiar partners

Table 2 Classification into a particular level of performance according to data from the Gross Motor Function Classification System (GMFCS)[26]

Level of Performance	Characteristics
I	The patient can walk freely
II	The patient walks on their own with certain (slight) limitations
III	The patient walks using ancillary equipment
IV	The patient can move on their own, but with certain limitations; he/she can use an electric wheelchair
V	The patient is not able to move on their own; he/she is transported in a wheelchair by a carer

TABELLA PER LA DETERMINAZIONE DEL LIVELLO CFCS



MACS

COSA E' NECESSARIO SAPERE PER UTILIZZARE IL MACS?

La competenza del bambino nel manipolare gli oggetti durante attività importanti della vita quotidiana, per esempio durante il gioco o lo svago, l'alimentazione o le operazioni di abbigliamento.

In quali situazioni il bambino è indipendente e fino a che punto ha bisogno di sostegno e di adattamenti?

I. **Manipola gli oggetti facilmente e con successo.** Possono esserci al massimo limitazioni nella facilità di esecuzione di compiti manuali che richiedono velocità ed accuratezza. Comunque qualunque limitazione nelle abilità manuali non restringe l'autonomia nella attività giornaliere.

II. **Manipola la maggior parte degli oggetti ma con una qualità non perfettamente buona e/o una certa lentezza nel concludere il compito.** Può succedere che alcune attività vengano evitate o eseguite con qualche difficoltà; possono essere utilizzate modalità alternative di esecuzione, ma le abilità manuali non limitano l'autonomia nelle attività quotidiane.

III. **Manipola gli oggetti con difficoltà; necessita di aiuto per predisporre e/o modificare le attività.** L'esecuzione è lenta e viene completata in modo non soddisfacente per quanto riguarda qualità e quantità. Le attività vengono eseguite autonomamente se sono state predisposte o adattate.

IV. **Manipola, in situazioni adattate, un numero limitato di oggetti facili da gestire.** Esegue una parte dell'attività con sforzo e con successo limitato. Richiede continuo sostegno ed assistenza e/o una situazione adattata, anche per eseguire una parte dell'attività.

V. **Non manipola oggetti ed ha competenze gravemente limitate nell'esecuzione anche di azioni semplici.** Richiede un'assistenza totale

DISTINZIONI tra livello I e II

I bambini a livello I possono presentare limitazioni nel manipolare oggetti molto piccoli, pesanti o fragili che richiedono un raffinato controllo della motricità fine, oppure un'efficiente coordinazione tra le mani. Le limitazioni possono riguardare anche la performance in situazioni nuove e non familiari. I bambini a livello II compiono quasi le stesse attività di quelli al livello I, ma la qualità dell'esecuzione è diminuita, oppure la prestazione è rallentata. Differenze funzionali tra le due mani possono limitare l'efficacia della performance. I bambini al livello II in genere cercano di semplificare la gestione degli oggetti utilizzando, per esempio, una superficie come appoggio invece di impegnare solo le due mani.

DISTINZIONI tra livello II e III

I bambini al livello II manipolano la maggior parte degli oggetti anche se lentamente o con ridotta qualità esecutiva. I bambini al livello III in genere hanno bisogno di aiuto per preparare l'attività e/o necessitano di adattamenti del contesto, poiché possiedono una limitata capacità di raggiungere o manipolare oggetti. Non riescono ad eseguire certe attività ed il loro grado di autonomia è correlato all'entità del supporto che offre il contesto.

DISTINZIONI tralivello III e IV

I bambini al livello III possono eseguire attività selettive se la situazione è predisposta, se sono assistiti e se hanno molto tempo a disposizione. I bambini al livello IV necessitano di costante aiuto durante l'attività e possono dare, al massimo, un significativo contributo solo ad una parte di essa.

DISTINZIONI tra livello IV e V

I bambini al livello IV eseguono parti di un'attività ma necessitano, comunque, di costante aiuto. I bambini al livello V, al massimo, possono partecipare in particolari situazioni facendo un semplice movimento, per es. premendo un bottone oppure possono, talvolta, mantenere la presa di oggetti facili da tenere.

Table 4 Modified Ashworth scale and Tardieu scale.

	Modified Ashworth scale	Tardieu scale
0	No increase in tone	No resistance throughout passive movement
1	Slight increase in tone giving a catch when slight increase in muscle tone, manifested by the limb was moved in flexion or extension	Slight resistance throughout, with no clear catch at a precise angle
1+	Slight increase in muscle tone, manifested by a catch followed by minimal resistance throughout the range of motion	
2	More marked increase in tone but more marked increased in muscle tone through most limb easily flexed	Clear catch at a precise angle followed by release
3	Considerable increase in tone, passive movement difficult	Fatigable clonus (< 10 s) occurring at a precise angle
4	limb rigid in flexion or extension (abduction, adduction, etc)	Unfatigable clonus (> 10 s) occurring at a precise angle

National Institute for Health and Care Excellence

Final Version

Cerebral palsy in under 25s: assessment and management

Full Guideline

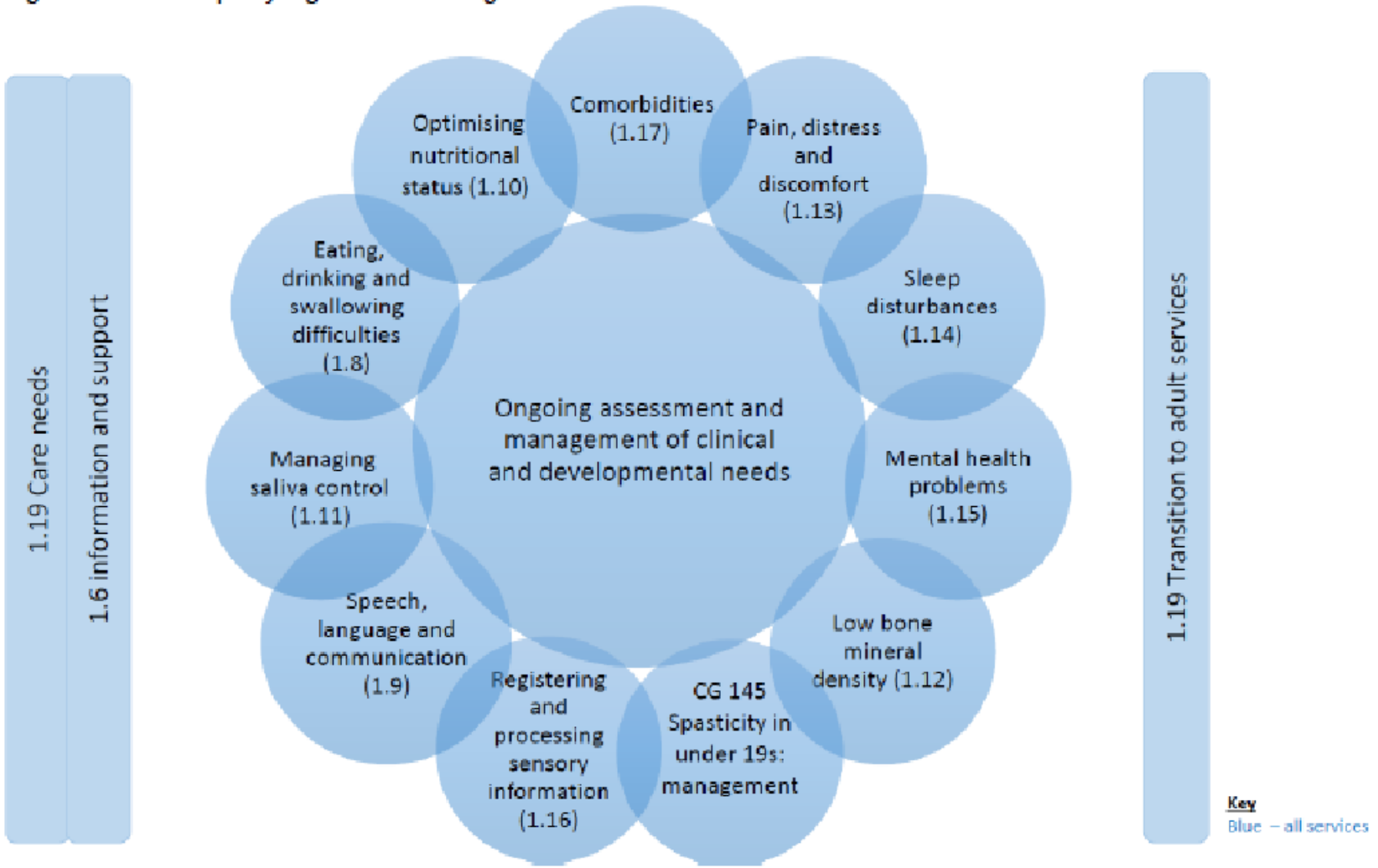
NICE Guideline NG62

Methods, evidence and recommendations

January 2017

Developed by the National Guideline Alliance, hosted by the Royal College of Obstetricians and Gynaecologists

Figure 2: Cerebral palsy algorithm – management



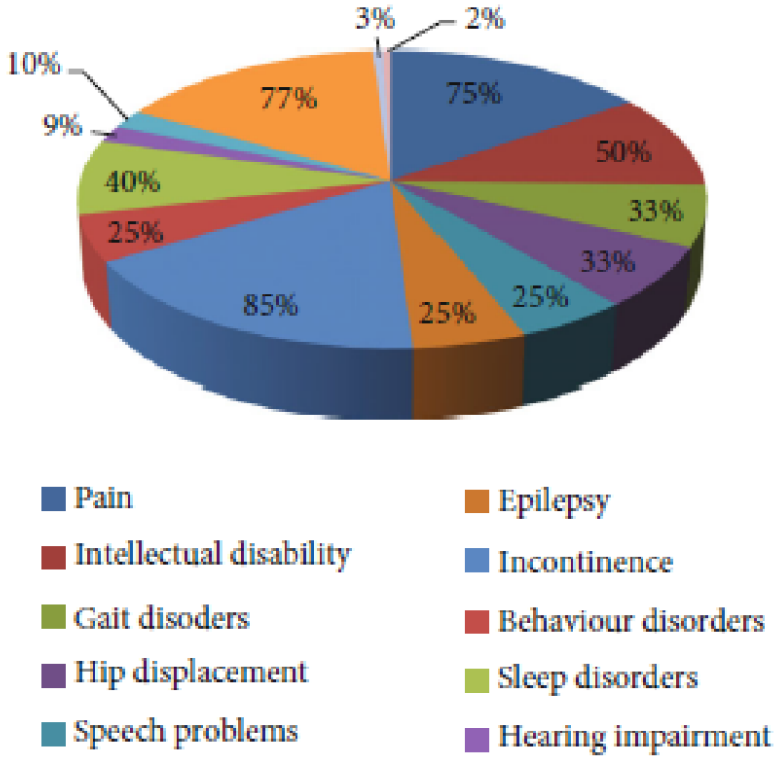


FIGURE 5: Comorbidities associated with cerebral palsy [11, 17–20].

Table 3 Proposed management, diagnostic tests and referrals to specialised care.

	Followup by coordinating paediatrician	Diagnostic tests	Referral to specialised care	
			Always	Based on condition
Neurologic disorders	Assess for epileptic seizures, intellectual disability, neuropsychiatric problems, movement disorders, language/speech disorders and spasticity	EEG in case of suspected epileptic seizures	Neurology Assist with integration and learning in school Rehabilitation Early intervention	
Orthopaedic disorders	Assess for fixed contractures and osteoarticular deformities			Traumatology/Neurosurgery in case of: Orthopaedic complications refractory to first-line treatment Surgical treatment of spasticity
Gastrointestinal disorders	Identify the caregiver in charge of feeding patient and ask how feeding is performed. Direct observation of mealtimes. Food frequency questionnaire. Specifically ask about symptoms related to: GOR Dysphagia Constipation Anthropometric evaluation: < 2 years: every 1–3 months > 2 years: every 3–6 months Combined use of specific growth charts for children with CP for sex and GMFCS level and WHO growth standards	Complete blood count, serum iron, ferritin, transferrin, calcium, magnesium, phosphate, albumin, total protein, liver enzymes, vitamins A, B12, D, E, folic acid, parathyroid hormone and zinc every year		Gastroenterology in case of: Undernutrition Suspected dysphagia GOR or constipation refractory to treatment
Bone health disorders	Food frequency questionnaire (calcium and vitamin D) every 6–12 m	Spine radiograph at 6–8 years, and every 2 years thereafter DEXA at 6 years if GMFCS level IV-V or younger with risk factors In case of supplementation with calcium and vitamin D, measure calcium, ionic calcium, phosphate, parathyroid hormone, vitamin D and alkaline phosphatase every 6 months		Rheumatology in case of: Osteoporosis Low BMD for age

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Table 3 (*Continued*)

	Followup by coordinating paediatrician	Diagnostic tests	Referral to specialised care	
			Always	Based on condition
Dental health	Regular checkups including oral examination and education on oral hygiene			Odontology in case of: Caries Gumboils Gingivitis Malocclusion
Respiratory disorders	Look for warning signs	Annual acid-base status		Pulmonology in case of: 6 years: lung function test Recurrent pneumonia Persistent wheezing Suspected sleep apnoea-hypopnoea syndrome Rehabilitation: Recurrent atelectasis Ear-nose-throat (ENT): Obstructive apnoea
Impaired vision	Look for warning signs Assessment with PREVIAS questionnaire (age < 2 years) and Dutton's Visual Skills Inventory (age > 5 years)		Ophthalmology	
Hearing loss	Complaint-directed history (family history of hearing loss, aetiology of CP, use of ototoxic drugs). Education of parents and teachers on hearing behaviour and language development. Look for warning signs			ENT in case of: Warning signs Recurrent acute otitis media (AOM) or persistent serous AOM
Urinary disorders	Complaint-directed history (bowel habits, urinary habits, history of urinary tract infection) Look for warning signs: Symptom diary: fluid intake, number and volume of voidings, bowel movements and incontinence episodes	Yearly workup. Renal function: urea and creatinine		Urology in case of: Recurrent urinary tract infection Warning signs

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(*Continued*)

	Followup by coordinating paediatrician	Diagnostic tests	Referral to specialised care	
			Always	Based on condition
Drooling	Management of sexual health Assess with Thomas-Stonell and Greenberg and Drooling Impact scales			
Sleep disturbances	Sleep diary			
Pain	Routine assessment of pain and exploration of pain triggers Assess with r-FLACC scale			
Psychosocial support	Inform primary care nurse			Social worker Child and adolescent mental health services
Care by paediatric palliative care and chronic complex disease team				Refer in case of: Clinical inflection point Symptoms that cannot be controlled with usual treatment Highly vulnerable patients with complex needs Difficulty with decision-making, need of guidance in treatment planning At discretion of paediatrician

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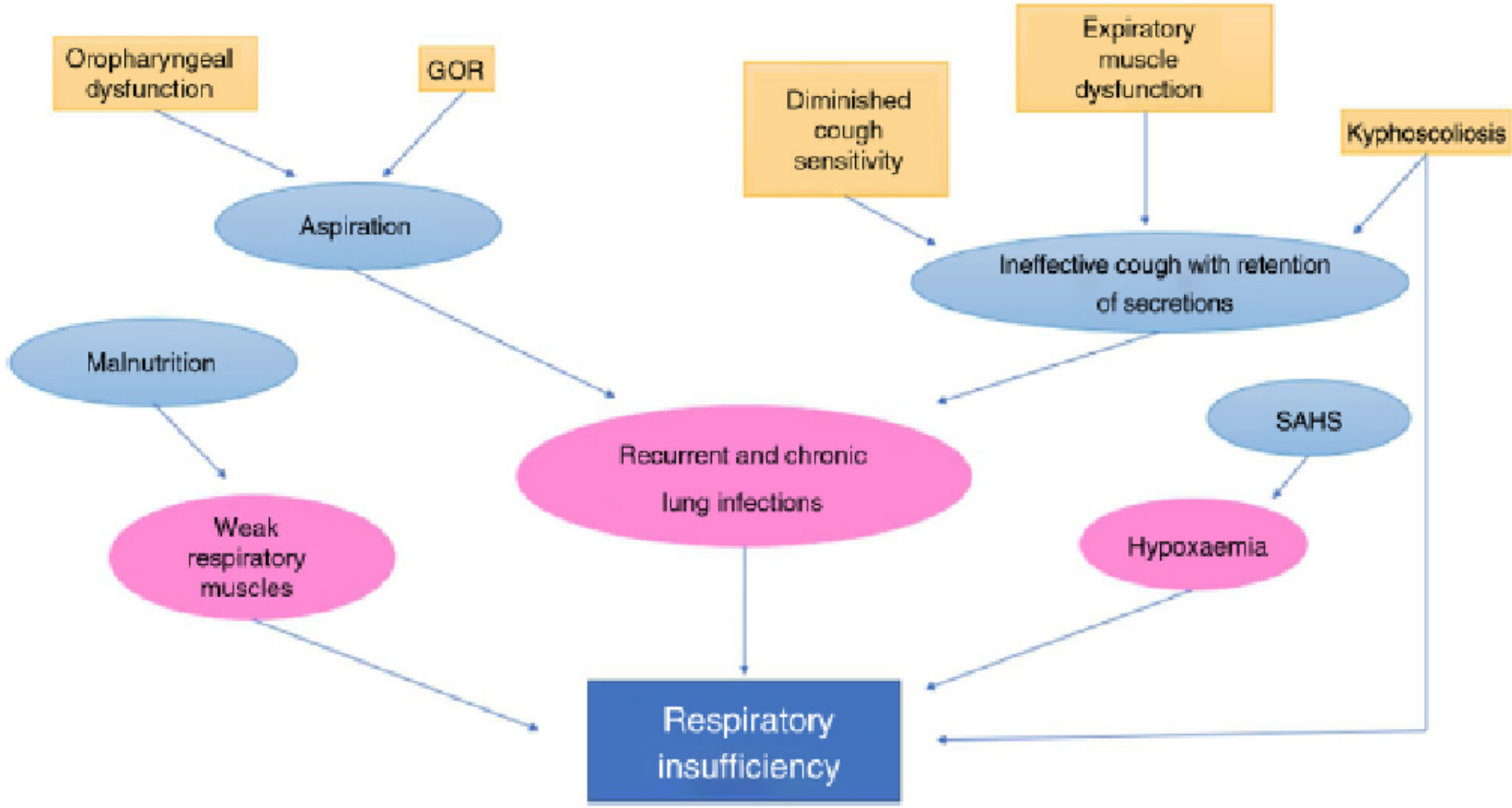

Figure 2 Factors involved in respiratory insufficiency in children with CP. GOR, gastro-oesophageal reflux; SAHS, sleep apnoea-hypopnoea syndrome.

Table 2 Drugs used most commonly in children with CP based on presenting problem and their dosage.

Movement disorder	
Trihexyphenidyl	Initial dose: 1 mg/day in 2 doses, with increases of 1 mg per week until reaching the effective dose or side effects develop. High doses (>10 mg/day) may be administered in 4 doses/day. Maximum of 2 mg/kg/day or 70 mg/day
Carbidopa-levodopa	Initial dose: 1 mg/kg/day in 3–4 doses, with progressive weekly increases (0.5–1 mg/kg) to a maximum of 10 mg/kg/day. Do not use doses >4–5 mg/kg/day in patients with CP
Spasticity	
Baclofen	*0.75–2 mg/kg/day given in 3–4 doses. Gradual increase until reaching:* 1 2 years: 10 20 mg/day in 4 doses (maximum, 40 mg/day) 2–6 years: 20–30 mg/day (maximum, 60 mg/day) > 6 years: 30–60 mg/day in 4 doses (maximum, 120 mg/day)
Clonazepam	Age >6 months to 10 years or to 30 kg body weight: initial dose of 0.01–0.03 mg/kg/day given in 2–3 doses. Slow gradual increase by 0.25–0.5 mg/week to 0.1 mg/kg/day up to a maximum dose of 0.2 mg/kg/day Age > 10 years: initial dose of 1–1.5 mg/day given in 2–3 doses. May be increased by 0.25–0.5 mg per week until individualised maintenance dose is reached. Maximum dose of 20 mg/day
Tizanidine	*0.1–0.2 mg/kg/day given in 2–3 doses. Generally, the recommended initial doses are:* 18 meses-7 years: 1 mg/day at night 7–12 years: 2 mg/day in 1–2 doses >12 years: dosage similar to adults, starting with 4 mg/day given in 2 doses (to a maximum of 36 mg/day)
Gastro-oesophageal reflux	
Omeprazole	0.6–3.5 mg/kg/day
Baclofen	0.7 mg/kg/day. Consider in case of associated spasticity
Constipation	
Polyethylene glycol	Initial disimpaction: 1,5 mg/kg/day in 1 or 2 doses Maintenance: 0.8 mg/kg/day in 1 or 2 doses
Lactulose	1–2 ml/kg/day in 1 or 2 doses
Bone health	
Calcium	1–3 years: 500 mg/day 4–8 years: 800 mg/day > 8 years- 18 years: 1300 mg/day
Vitamin D	Age < 1 year: 800 IU-1000 IU Age ≥ year: 800 IU-4000 IU
Bladder dysfunction	
Oxybutynin	0.1–0.4 mg/kg/day (maximum 15 mg/day)
Desmopressin	120–240 μg/day 30 min before bed
Drooling	
Glycopyrronium bromide	1 month-17 years: initial dose of 0.02 mg/kg every 12 h. In case of poor response, it can be given every 6–8 h. The dose can later be increased by 0.02 mg/kg/dose to 0.1 mg/kg/dose. Maximum dose, 0.1 mg/kg/dose or 2 mg/dose
Scopolamine	Apply patches under or behind the ear. First week: ¼ patch, second week: ½ patch, third week: ¾ patch, fourth week: full patch. Change every 3 days, alternating ears: Neonates > 32 semanas-2 years: ¼ patch every 72 h 3–9 years: ½ patch every 72 h >10 years: 1 patch every 72 h
Trihexyphenidyl	Initial dose: 0.1 mg/kg/day in 3 doses, in case of a weak effect, increase progressively in weekly steps to 0.5 mg/kg/day (maximum dose, 10 mg/day)

Table 2 (*Continued*)

Sleep disturbance	
Melatonin	3–15 mg/day
Lorazepam	0.05–0.1 mg/kg/dose (maximum 2–4 mg/dose)
Zolpidem	Age > 2 years: 0.25 mg/kg/day (maximum 5–10 mg)

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PEDIATRIC NEUROLOGY (WE KAUFMANN, SECTION EDITOR)

State of the Evidence Traffic Lights 2019: Systematic Review of Interventions for Preventing and Treating Children with Cerebral Palsy

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Published online: 21 February 2020

Abstract

Purpose of Review Cerebral palsy is the most common physical disability of childhood, but the rate is falling, and severity is lessening. We conducted a systematic overview of best available evidence (2012–2019), appraising evidence using GRADE and the Evidence Alert Traffic Light System and then aggregated the new findings with our previous 2013 findings. This article summarizes the best available evidence interventions for preventing and managing cerebral palsy in 2019.

Recent Findings Effective prevention strategies include antenatal corticosteroids, magnesium sulfate, caffeine, and neonatal hypothermia. Effective allied health interventions include acceptance and commitment therapy, action observations, bimanual training, casting, constraint-induced movement therapy, environmental enrichment, fitness training, goal-directed training, hippotherapy, home programs, literacy interventions, mobility training, oral sensorimotor, oral sensorimotor plus electrical stimulation, pressure care, stepping stones triple P, strength training, task-specific training, treadmill training, partial body weight support treadmill training, and weight-bearing. Effective medical and surgical interventions include anti-convulsants, bisphosphonates, botulinum toxin, botulinum toxin plus occupational therapy, botulinum toxin plus casting, diazepam, dentistry, hip surveillance, intrathecal baclofen, scoliosis correction, selective dorsal rhizotomy, and umbilical cord blood cell therapy.

Summary We have provided guidance about what works and what does not to inform decision-making, and highlighted areas for more research.

Keywords Cerebral palsy · Systematic review · Traffic light system · Evidence based · GRADE

RACCOMANDAZIONI PER LA RIABILITAZIONE DEI BAMBINI AFFETTI DA PARALISI CEREBRALE INFANTILE

Aggiornamento 2013

SOCIETA' ITALIANA DI MEDICINA FISICA E RIABILITAZIONE (SIMFER)
SOCIETA' ITALIANA DI NEUROPSICHIATRIA DELL'INFANZIA E DELL'ADOLESCENZA (SINPIA)

Table 1
Oral medications for management of spasticity/dystonia

Use	Generic Name	Dosage	Mechanism of Action	Side Effects
Spasticity/ dystonia	Baclofen	Start 2.5 mg TID, maximum dose 80 mg/d divided TID in children >8 y/o	GABA B agonist	Sedation (but less than benzodiazepines), constipation
Spasticity/ dystonia	Clonazepam	0.01–0.3 mg/kg/d divided BID or TID	GABA A agonist	Sedation, drooling, constipation
Spasticity	Clonidine	Start at 0.05 mg/d and increase by 0.05 mg every week to a maximum of 0.3 mg/d divided TID	Central-acting alpha-2 adrenergic agonists	Sedation, hypotension, bradycardia
Spasticity/ dystonia	Dantrolene	0.5 mg/kg divided BID, increase every week to a maximum of 12 mg/kg/d divided QID	Interferes with release of calcium from sarcoplasmic reticulum in skeletal muscles	Weakness, sedation (but less than others), hepatotoxicity
Spasticity/ dystonia	Diazepam	0.05–0.1 mg/kg/d divided BID to QID	GABA A agonist	Sedation, constipation, urinary retention
Spasticity	Gabapentin	Start 10–15 mg/kg/d divided TID, titrate maximum of 60 mg/kg/d divided TID	Unknown	Sedation, emotional lability
Dystonia	Carbidopa/levodopa	25/100: start 0.25–0.5 tablet BID, maximum 800 mg/d divided BID or TID	Dopamine precursor, indirect receptor agonist	Rarely effective in CP, more effective in genetic dystonia GI upset; may add extra carbidopa (Lodosyn) to alleviate side effects, sedation
Spasticity/ cramps	Tizanidine	Start 1–2 mg QHS with maintenance 0.3–0.5 mg/kg/d divided TID or QID	Central-acting alpha-2 adrenergic agonists	Sedation, hypotension, hepatotoxicity
Dystonia	Trihexyphenidyl	Start 2–2.5 mg/d, increase by 2–2.5 mg every other week to maximum dose of 60 mg/d divided BID or TID	Anticholinergic	Sedation, constipation, urinary retention, dry mouth, dyskinesias, motor tics

Abbreviations: BID, twice a day; GI, gastrointestinal; QHS, at bedtime; QID, 4 times a day; TID, 3 times a day.

McMaster Children's Hospital
HAMILTON HEALTH SCIENCES

Inventory List of Goals in the Context of Botulinum Toxin A Treatment

McMaster University
Department of Pediatrics

Participant's GMFCS Level: _____

Please read the following and mark the boxes beside the description that best represents the body structure and function, activity, and participation that you would you like your child to achieve after botulinum toxin treatment.

I would like the botulinum toxin treatment to help my child to...

Body Structure / Function	Activity	Participation
Body Structure **Improve Range of Motion** □ In the legs □ and straighten the hips □ and straighten the knees □ and straighten the ankle □ In the arms □ and raise the shoulders □ and straighten the elbows □ and straighten the wrists □ and bend and flex the fingers **Function** □ Reduce overall muscle tone □ Reduce the amount of drooling □ Reduce the feeling of generalized pain □ Increase bone health and strengthen bones □ Sleep with few disturbances	□ Increase mobility □ and walk for longer distances □ and stand for longer periods of time □ Facilitate ease of transfers in position (ex. from bed to chair) by care provider □ Sit comfortably and with good posture □ Be able to use assistive equipment □ and use a walker □ and use a wheelchair □ and use a stander □ Tolerate braces □ and wear braces for a longer period of time □ Tolerate exercise □ and be able to do stretching exercises □ Manipulate and use small objects with hands (e.g. writing supplies such as a pencil, light switches) □ Manage personal hygiene (e.g. diapering, toileting) □ By patient □ By care provider □ Change clothes □ and facilitate ease of dressing (e.g. socks, pants) □ By patient □ By care provider □ and reduce the time taken to put on clothes □ By patient □ By care provider □ Eat meals □ and provide easier use of utensils □ and reduce the time taken to eat meals	□ Be able to participate and compete □ In wheelchair sports □ Recreational activities □ Swimming □ Biking □ Community groups □ School activities □ Religious activities

Fig. 2. Goal inventory for botulinum toxin treatment. (*From* Nguyen L, Mesterman R, Gorter JW. Development of an inventory of goals using the International Classification of Functioning, Disability and Health in a population of nonambulatory children and adolescents with cerebral palsy treated with botulinum toxin A. BMC Pediatr. 2018;18:1.)

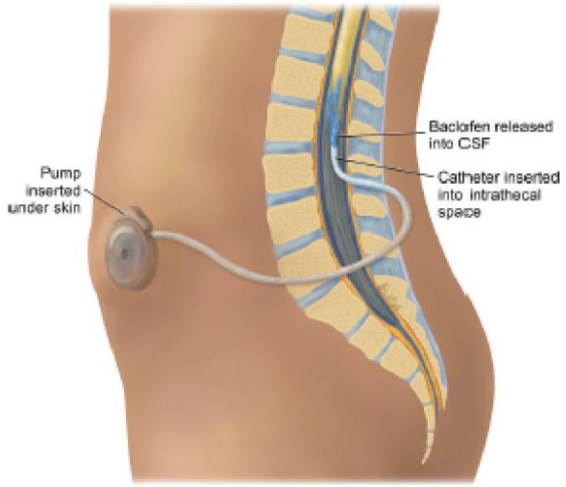

Fig. 1 Intrathecal baclofen involves a catheter being inserted into the intrathecal space preventing pain signals from reaching the brain

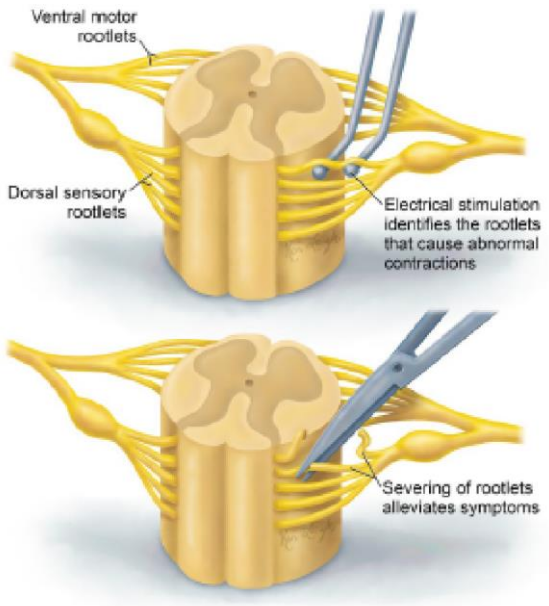

Fig. 2 Selective dorsal rhizotomy is a surgical procedure that involves the severing of lumbosacral sensory nerves in the spine to relieve pain

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REVIEW

Intrathecal baclofen, selective dorsal rhizotomy, and extracorporeal shockwave therapy for the treatment of spasticity in cerebral palsy: a systematic review

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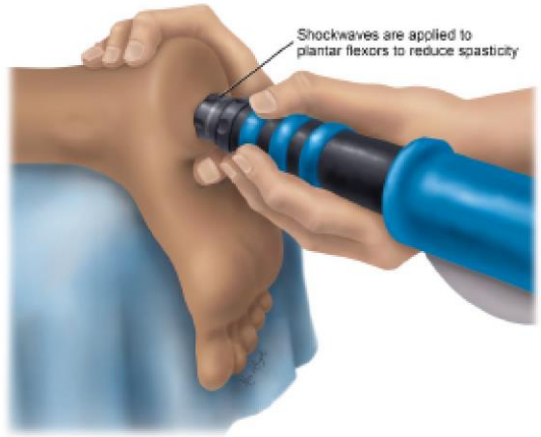

Fig. 3 In extracorporeal shockwave therapy, electric shocks of varying frequencies at different time intervals provide relief of spastic muscle pain

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L'innovazione è stata presentata oggi al San Raffaele di Roma: si chiama 'Atlas 2030'. Permetterà ai bimbi affetti da diverse patologie di camminare e fare altre attività