Aetiological Pathways of Cerebral Palsy

Paediatric Neurology and Developmental Association of Southern Africa

June 2022

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Why is it important to particularly important to understand risks to brain development in LMICs?

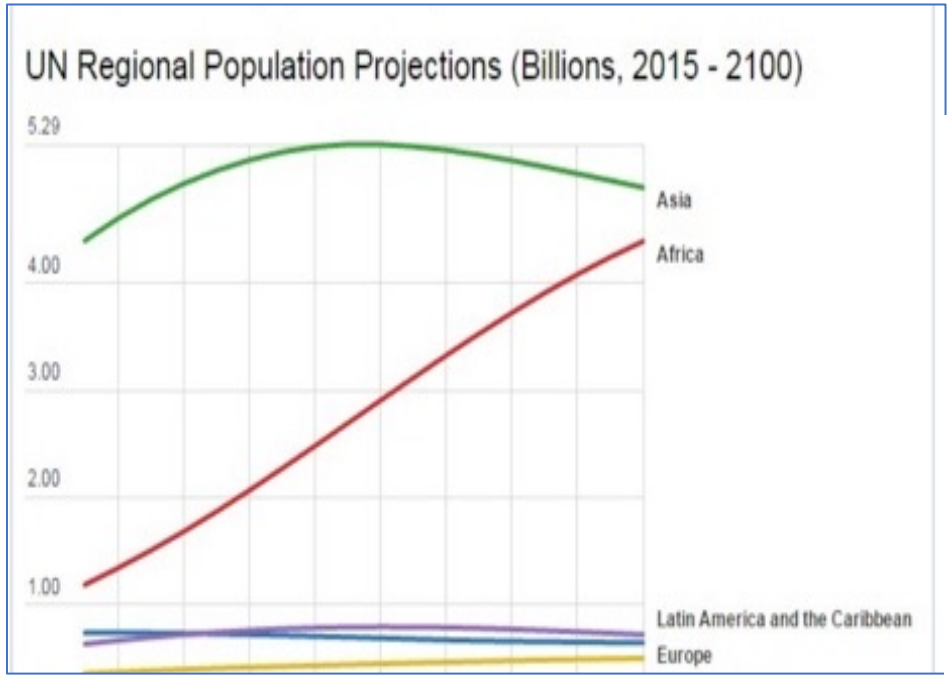
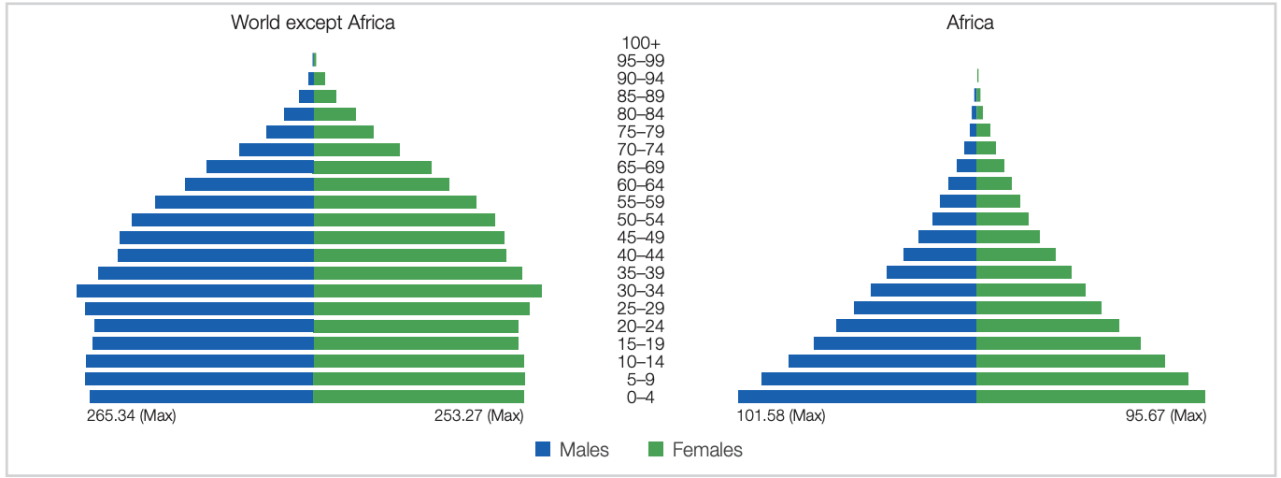


Figure 5: Population age structure – Africa vs rest of the world

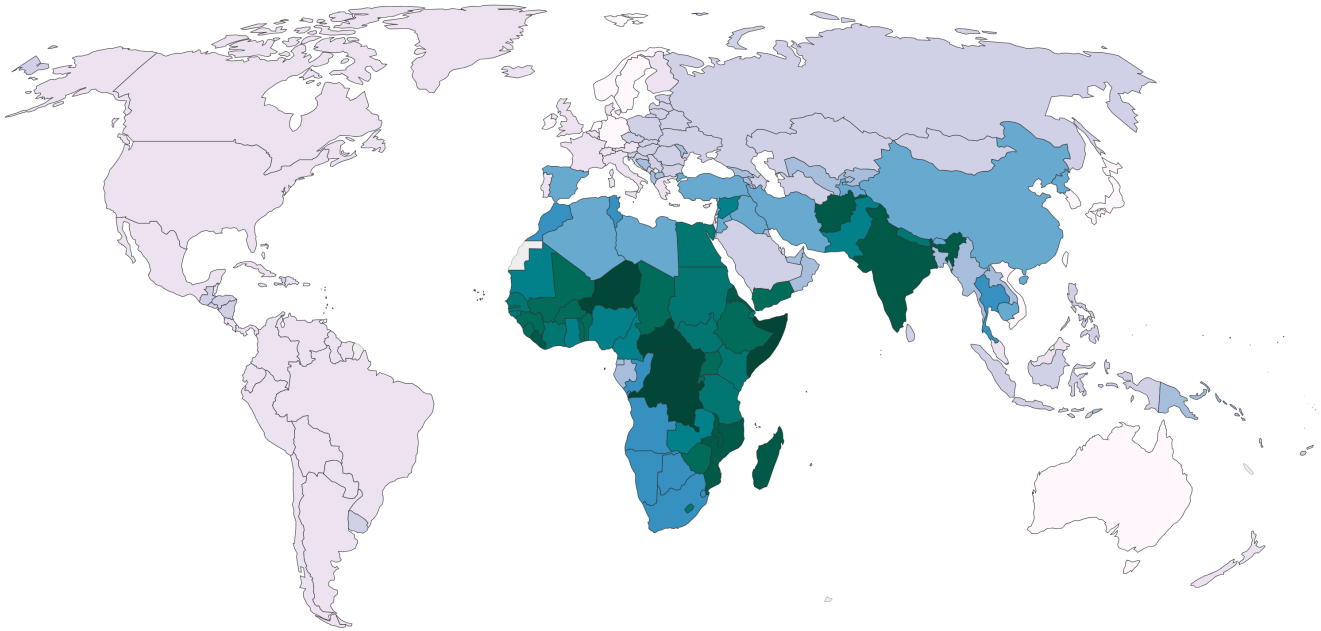


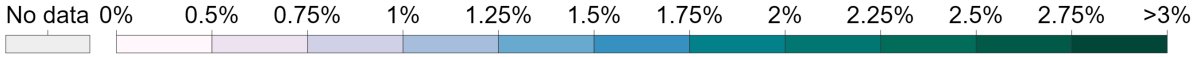
Source: IFs v7.45 initialising from UN Population Division data

Share of population with developmental intellectual disability, 2016

Share of the population with 'idiopathic developmental intellectual disability' which is a category of disorders defined by delayed or impaired speech, language, motor condition, and visuo-spatial skills. Prevalence has been age-standardized to compare between countries and with time.

Our World in Data





Children will remain the major focus of Africa and Africa will be the main focus of the world's children

Hence the crucial importance of neurodevelopment – understanding all the factors that contribute to healthy child brain development and function

In 2050 of Africa's projected 2.9 billion population, 1 billion will be children under 18 (i.e. 35%)

Children in Africa will account for nearly 40% of the world's children under 18 in 2050 rising to a staggering 49% of all the world's children by 2100

Defining Cerebral Palsy

Group of permanent neuromotor disorders characterized by abnormal movement, muscle tone, and posture

Caused by abnormal brain development or damage to the developing brain

- Most common underlying pathophysiology: injury to developing the foetal or neonatal brain (Congenital CP)
- Post-neonatal CP (Acquired CP)
  - Injury to developing brain after the neonatal period and before 2 years of age

Symptoms vary according to a spectrum of severity

Non-progressive symptoms vs. secondary conditions

Common comorbidities: Intellectual disability, seizures, secondary musculoskeletal disorders (e.g. scoliosis, contractures), difficulty with vision, hearing, or speech

Centre for Disease Control (CDC; 2022), Patel et al (2020), Sadowska et al (2020)

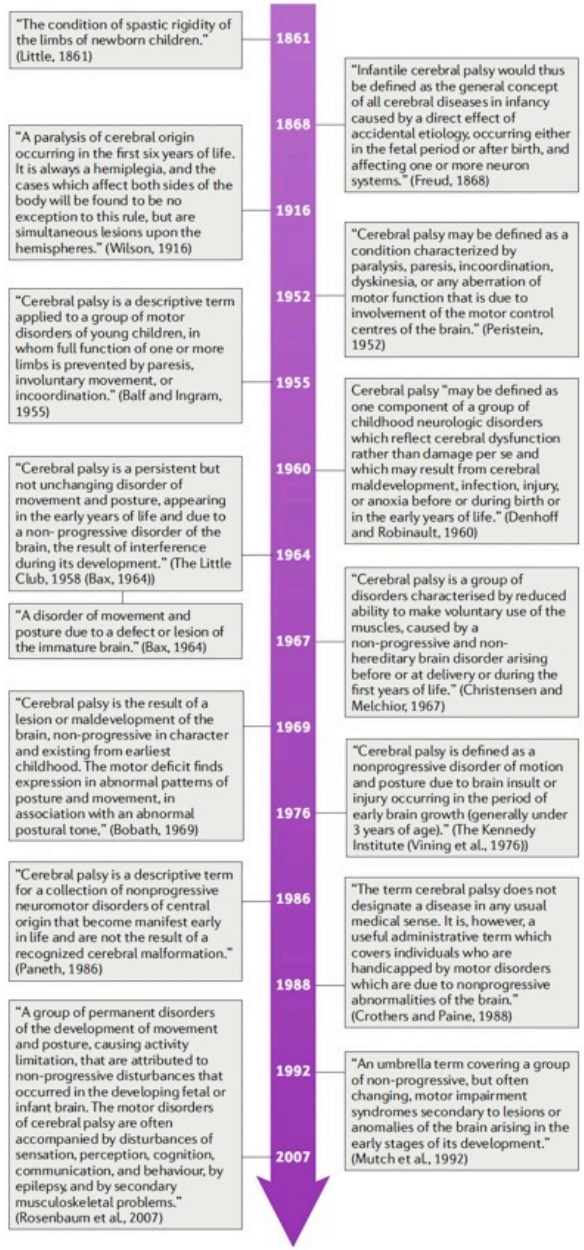


Fig. 1 | **Definitions of cerebral palsy over time.** The definition of cerebral palsy has changed several times since 1861, and the most recent definition was described in 2007.

Cerebral Palsy is a clinical syndrome

Clinically classified based on predominant motor condition

Four types of movement disorder

- Spastic CP
  - Most common (80% of individuals with CP)
  - Characterized by increased muscle tone
  - Diplegia/diparesis, hemiplegia/hemiparesis, quadriplegia/quadriparesis
- Dyskinetic/Dystonic CP
  - Different types of voluntary movement abnormalities or involuntary movements of arms, legs, hand, feet, face, and/or tongue
  - Slow and writhing vs. rapid and jerky
- Ataxic CP
- Mixed CP
  - Features of multiple CP types
  - Most common: Spastic-Dyskinetic

Severity

Gross Motor Function Classification System (GMFCS; 5 levels)

MACS, EDACS….focus on function

Global Prevalence of CP

Most common cause of physical disability in children (Donald et al., 2015)

Globally: 17 million people with CP (Graham et al., 2016)

National CP registers and population-based studies: 1.8 – 2.5 cases per 1000 children

- Australia (Smithers-Sheedy et al., 2016)
- Europe (Sellier et al., 2016)
- USA (Van Naarden-Braun et al., 2016)
- Canada (Oskui et al., 2013)

Global prevalence largely based on research from HICs

Population prevalence in Africa

Uganda: 2.4 – 3.6 per 1000 children (Kakooza-Mwesige et al., 2017)

Nigeria: 2.3 per 1000 children (Duke et al., 2020)

South Africa: Estimated to be as high as 10 per 1000 births (Couper, 2002)

Call for an official registry (Katangwe, 2020)

Prevalence and Presentation in LMICs

Very few registers and population-based studies of CP in LMICs (Katangwe et al, 2020)

CP prevalence in LMICs > HICs (*Duke et al., 2020; Kakooza-Mwesige et al., 2017; Khandaker et al., 2019)*

- Different or greater risk (Donald et al., 2014)
  - Preterm birth
  - Obstetric complications
  - Birth asphyxia
  - Cerebral infections
  - Seizures
- High mortality rate
- Survival bias underestimates prevalence

Prevalence and Presentation in LMICs

Establishment of more CP registers in LMICS over recent years

Bangladesh CP Register (BCPR)

- First population-based CP registers (Khandaker et al., 2015)
- First LMIC population-based prevalence from BCPR: 3.4 per 10000 live births (Khandaker et al., 2019)

Global LMIC CP Register (GLM-CPR) developed (Jahan et al., 2021)

- Multi-country initiative combining CP data in children <18y
- Recent data from Bangladesh, Nepal, Indonesia, Ghana:
  - 86.6% of children in LMICs acquire CP pre and perinatally
  - Median age of diagnosis: 3 years
  - 79.2% with spastic CP, 73.3% with GMFCS levels III-V
  - 47.3% never received rehabilitation services
  - 75.6% of school-age children with no access to education

Aetiology of CP global understanding

Traditional discrete approaches

- e.g. Birth asphyxia, prematurity, kernicterus, meningitis

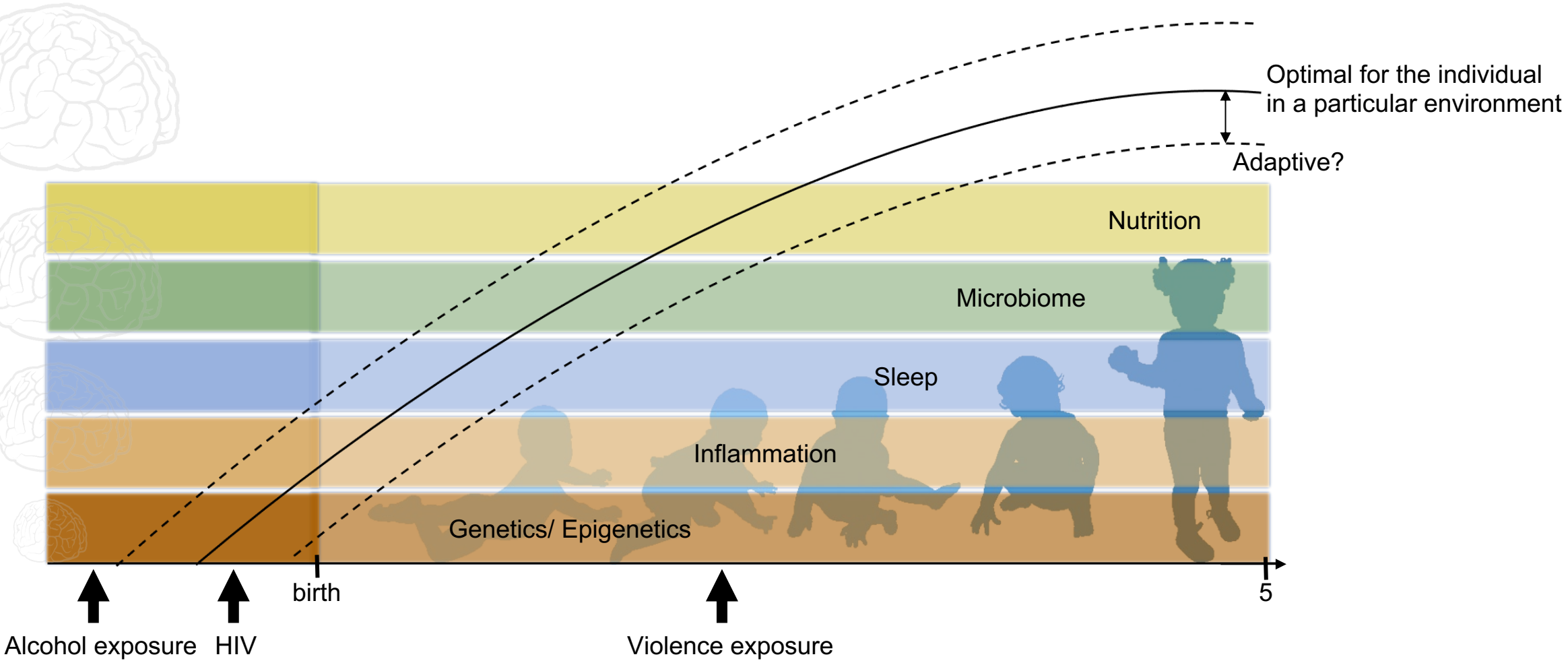
Newer considerations based on understanding of risk

- role of genetic risk
- role of inflammation and immune dysregulation
- role of hormonal regulation (thyroid, iodine, cortisol)

Complexity of interaction and timing

A clear aetiological factor may be identified, but its effects may have played out differently in different children

Developmental Brain Trajectory



Key points

- Several high-income countries have reported a decline in the prevalence of cerebral palsy (CP); therapeutic hypothermia and magnesium sulfate for neuroprotection might have played a role, but other factors might be important.
- The minimum age at which CP can be reliably diagnosed is controversial; evidence that early diagnosis and intervention improves motor outcome is sparse, but there are hints of benefits for cognitive outcomes.
- No consensus exists about CP subtypes; the general term CP is important for public health and health services planning, but subtypes might have different aetiologies.
- Gestational age and birthweight have been a major focus of CP investigators; to move forward, we must seek a deeper understanding of why these factors convey information about increased risk.
- Preconception factors, including maternal obesity and age, should be considered because they can modify the relationships between CP and other factors that occur later in pregnancy.
- Two-hit and multi-hit models that consider accumulation of risk factors can identify a synergistic increase in the risk of CP, but the time order and clinical relevance of the model components must be established.

Approaches to Aetiology

Guidelines for early diagnosis (Novak et al., 2017)

- **Medical history, standardized neurological and motor examination/assessments, neuroimaging**
- Brain Imaging (Towsley et al., 2011)
  - Neuroimaging: Standard evaluation in children with CP
  - Population-based registry: Cerebral imaging abnormalities in 86.9%
    - Periventricular white matter (19.2%)
    - Diffuse grey matter injury (14.6%)
    - Cerebral vascular accident (11.7%)
    - Cerebral malformation (11.3%)
  - Specific patterns of neuroimaging associated with neurological subtype, CP severity (i.e. GMFCS Level), other categorical variables.

What makes neuroimaging more challenging in our practice?

Child and family factors

- difficult to contact
- families may have less work flexibility
- lack of reliable transport
- lack of familiarity with hospital environment
- value of the investigation

Medical environment

- fewer imaging facilities available
- pressure on the facilities
- expertise is scarce
- cost of imaging

TABLE 1. Clinical features that should prompt evaluation for genetic and metabolic conditions in a patient presenting with symptoms of CP

Absent history of any perinatal risk factor for brain injury
Family history of sibling with similar neurological symptoms
Motor symptom onset after an initial period of normal development
Developmental regression
Progressive neurological symptoms
Paroxysmal motor symptoms or marked fluctuation of motor symptoms
Clinical exacerbation in the setting of a catabolic state (e.g., febrile illness)
Isolated generalized hypotonia
Prominent ataxia
Signs of peripheral neuromuscular disease (reduced or absent reflexes, sensory loss)
Eye movement abnormalities (e.g., oculogyria, oculomotor apraxia, or paroxysmal saccadic eye-head movements)

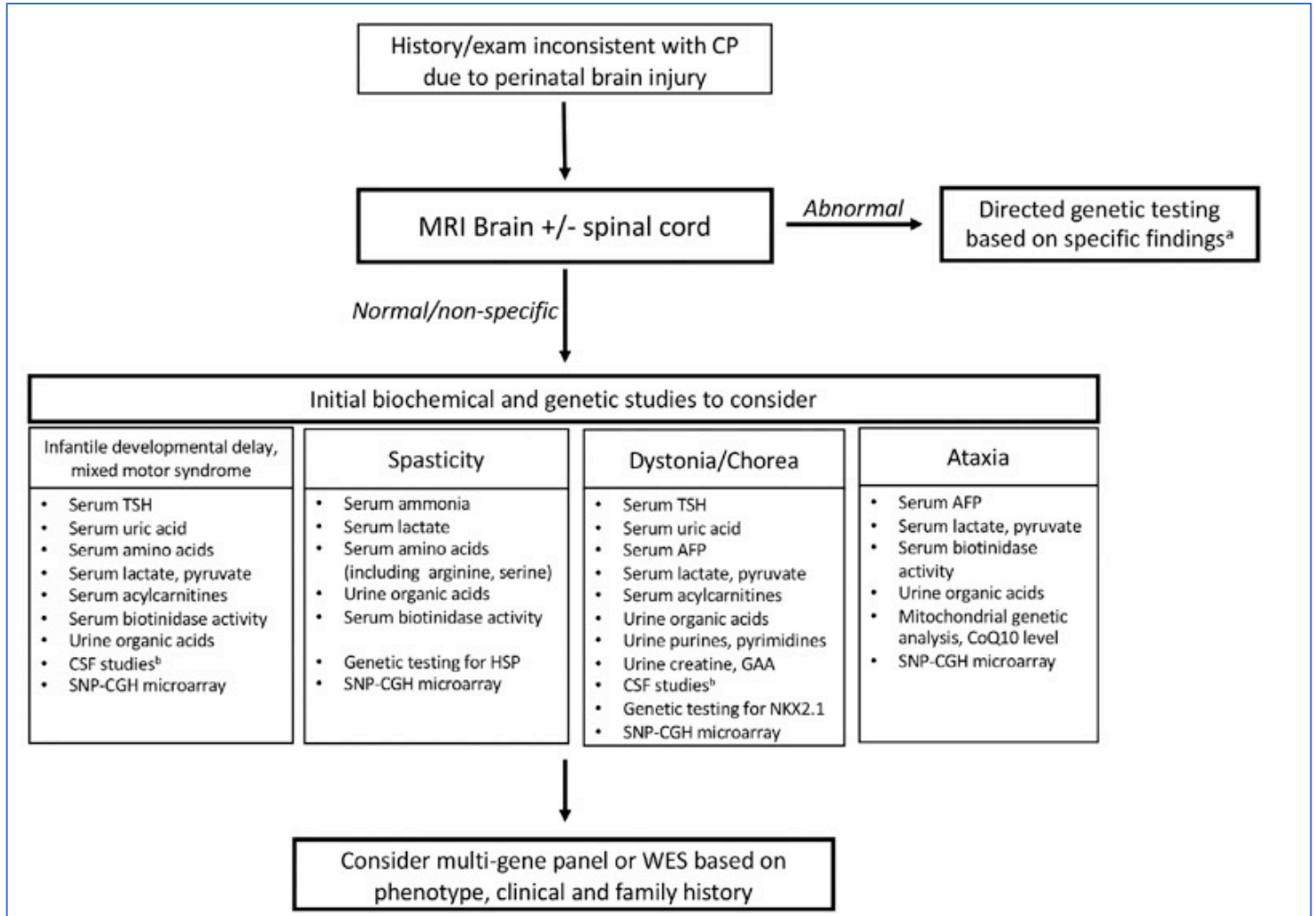


FIG. 1. General diagnostic approach to the patient with an infantile-onset, apparently non-progressive motor disorder. Studies are grouped by predominant clinical presentation; it may be appropriate to consider investigations from more than one group depending on the specific clinical context. [a] See examples in Table 2 [b] CSF studies: glucose (+serum glucose), lactate, pyruvate, neurotransmitter metabolites (biogenic amines + GABA), pterins, 5-methyltetrahydrofolate.

Investigations cont

Genetics (Emrick et al., 2020)

- Scope of CP diagnosis includes genetic disorders (e.g. genetic metabolic disorders)
- >800 genetic conditions that include CP in phenotype
- Patients with atypical CP presentations (normal neuroimaging, progressive course, family hx) considered for genetic work-up
- Susceptibility genes for CP
- Be aware of genetic conditions that mimic CP motor phenotypes

“mimics”

- CP is a syndromic diagnosis
- Disagreement on what falls under this umbrella

TABLE 2. Brain MRI findings suggestive of selected genetic CP mimics

Finding	Selected Conditions
Hypomyelination	*PLP1*-related dysmyelinating disorders H-ABC (*TUBB4A* mutation) AGS (may also have basal ganglia and WM calcification) GM1 gangliosidosis
Demyelination	Krabbe disease Metachromatic leukodystrophy
Thin corpus callosum	HSP (i.e., SPG4, SPG11, SPG15, and others)
Globus pallidus lesions	T_2-hypointense: NBIA (SN also involved in BPAN, MPAN), fucosidosis T_2-hyperintense: MMA, PDH deficiency, creatine deficiency syndromes
Focal atrophy or hypoplasia	Glutaric aciduria type 1 (frontotemporal), H-ABC (cerebellum ± putamen), Joubert syndrome (cerebellum)

AGS, Aicardi-Goutières syndrome; BPAN, beta-propeller protein-associated neurodegeneration; H-ABC, hypomyelination with atrophy of the basal ganglia and cerebellum; MMA, methylmalonic aciduria; MPAN, mitochondrial membrane protein-associated neurodegeneration; NBIA, neurodegeneration with brain iron accumulation; PDH, pyruvate dehydrogenase; WM, white matter.

Aetiology of CP in LMICs

Bangladesh: 726 CP children CP, 4.8mo – 18y (Khandaker et al., 2019)

- Preventable risk factors
  - Prenatal/perinatal (62%): Neonatal respiratory distress, encephalopathy, infections
  - Postnatal (6%): Trauma, infections, drowning
- Mean age at CP diagnosis: 5 years, 2 months

Aetiology of CP in Africa

Uganda: 86 children with CP; aged 2-17 years (Kakooza-Mwesige et al., 2017)

- High prevalence of severely affected children (GMFC levels 4-5)
- Only 2% of CP children were born pre-term (low survival)
- Post-neonatal events responsible for 25% of cases: Cerebral malaria and seizures

Nigeria: 388 children with CP; aged 4-15 years (Duke et al., 2020)

- Prenatal/perinatal risk factors in 63.9% of children: birth asphyxia, congenital rubella, hyperbilirubinemia
- Post-neonatal risk factors in 36.1% of children: Malaria, seizure, meningitis, tuberculosis, sickle cell disease, HIV

Benin: 114 children with CP between ages 2-17 years (Sogbossi et al., 2019)

- Most children were severely affected (67.5% as bilateral spastic; 54.4% as GMFCS 4 or 5)
- High percentage of perinatal risk factors (induced labour, birth complications)
- Only 7% CP children pre-term
- 17% of children had post-neonatal CP

CP : Global vs Local

Different Pattern of Risk and Aetiology

- Fewer preterm cases of CP in this context due to high mortality of premature babies in LMICs
    - 2-7% in LMICs vs. 40% in HICs
- Higher proportion of post-neonatal CP (acquired) due to increased postnatal risk factors such as infection

Increased burden of disability

- Higher number of severe cases of CP
    - Spastic CP most common
    - Gross Motor Function Classification System level 4–5
- High rate of comorbidities

High high mortality during the first 6–8 years of life, particularly among the most severely affected

Duke et al., 2020; Kakooza-Mwesige et al., 2017; Khandaker et al., 2019; Sogbossi et al., 2019

Challenges in LMICs

Increased prevalence of CP in LMICs: increased risk factors affecting foetal and postnatal brain development

- Preventable risk factors in resource-limited settings
- Underestimated by lack of registries and high mortality rates

Increased burden of disability

- Higher proportion of severe CP cases
- Increased rates of comorbidities

Poor screening and delayed diagnosis

- Limited resources and diagnostic facilities
- Difficulty distinguishing between CP and mimics

Limited services

- Limited access to healthcare and specialists (Andrews et al., 2020; Jahan et al., 2021)
- Lack of rehabilitation (Al Imam et al., 2021)
- Lack of adaptive equipment (e.g. wheelchairs and ambulation aids; Njambi et al., 2009)
- High levels of Social stigma (El Tallawy et al., 2010)
- Lack of wheelchair accessible transport (Hartley et al., 2005)
- Limited access to special-needs schools (Andrews et al., 2020; Jahan et al., 2021)

Next Steps: CP in LMICs

Establishment of CP registers in LMICs

Publication of population-based studies on CP

Addressing preventable risk factors for CP

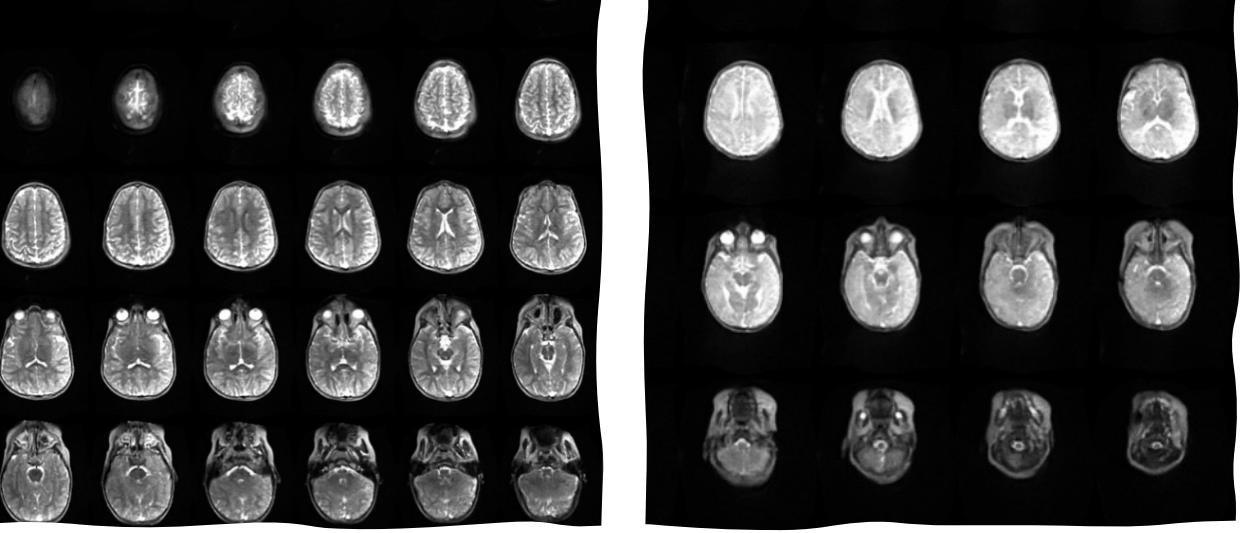
- Decrease CP prevalence
- Reduce mortality rates
- Lower severity and risk of comorbidities

Identifying appropriate and accessible tools

- Investigating the efficacy of new technologies

Improving the accessibility of services:

- Healthcare
- Rehabilitation and assistive devices
- Education



Considerations of new low-cost technologies to support understanding aetiological pathways and monitoring interventions

Thank You

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