

UNIT NO. 2

DISEASES THAT RESULT IN DISABILITY IN INFANTS AND CHILDREN

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ABSTRACT

Disability in children can be broadly classified into physical and mental disabilities, and there are many conditions that result in this. Some diseases result in only physical or mental disability. Physical disability is often present in children with cerebral palsy or neuromuscular disorders. With mental disability, the children are not able to learn self help skills and remain dependent on their caregivers for most of the activities of daily living. An extension of this group would include those with moderate to severe autism. In paediatrics, many conditions result in both forms of disabilities, with greater consequence and burden to their families. Long term care and rehabilitation remains the most challenging task for all involved in the care of disabled children.

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INTRODUCTION

Disability in infants and children can be broadly categorised into physical and mental disabilities, with some neurological conditions having a combination of both.

Some of the common paediatric conditions associated with significant physical disabilities are cerebral palsy, neuromuscular diseases such as muscular dystrophy, and spina bifida. The universal problems faced by the patient and caregivers include ambulation or mobility, as well as activities of daily living. Some of these children also have cognitive dysfunction, making rehabilitation and long term care a much more challenging task. The comprehensive management of children with physical disabilities include regular physical therapy, use of orthotic appliances (splints), and appropriate ambulatory aids such as rollators or Kaye-walkers, quadsticks and elbow crutches. Inputs from the occupational therapist together with the use of appropriate assistive device, such as splints and Lycra body suits, may help towards functional gains in the motor skills.

For children with mental disability, there is significant limitation in intellectual functioning, and adaptive behaviour as expressed in conceptual, social, and practical adaptive skills. Mental retardation, as confirmed through standardised tests of intelligence and adaptive behaviour, is thought to be present if a child has an intelligent quotient (IQ) score of 70 or below, with a significant deficit in at least one area of adaptive behaviour¹. For most of these infants with global developmental delay and children with mental disability, the early intervention programme in at-risk children (EIPIC), followed by special education using individualised education

programmes, serve to maximise their educational potential. For autistic children with problems in social interaction and communication as well as marked restriction of interests and activities, special education is available in special schools and resource centres. There is some evidence for the use of intensive applied behavioural analysis² in the kindergarten and school setting to help ameliorate some of the autistic behaviours, as well as improve the IQ and adaptive functioning.

CONDITIONS WITH PHYSICAL DISABILITY IN INFANTS AND CHILDREN

The common paediatric conditions associated with significant physical disability can be divided broadly into those that occur as a consequence of early brain injury resulting in cerebral palsy, paediatric neuromuscular diseases which are often progressive such as muscular dystrophy, and developmental abnormalities in the spinal cord as in spina bifida cystica or spinal dysraphism. Besides these, rare neurodegenerative and metabolic disorders can also result in progressive physical and mental disabilities.

CEREBRAL PALSY

Cerebral palsy (CP) or static encephalopathy, is defined as a disorder of posture and movement secondary to a non-progressive lesion or insult to the developing brain. The “umbrella term” of CP refers to children with a wide range of static cerebral disorders associated with motor impairment³. Most studies report a prevalence rate of about 2 per 1000 children at 7 to 10 years of age, with moderate to severe mental retardation present in 20 to 30% of these children. In addition, there could also be concomitant specific deficits or impairments in vision, hearing or speech. The type of CP is categorised by the pattern of motor involvement depending on which brain structure in the most affected, i.e. spastic (cerebral cortex), dyskinetic (basal ganglia), ataxic (cerebellum), and mixed. In the mixed form, an ataxic or dyskinetic CP coexists with a spastic CP subtype. The subtypes of spastic CP are further classified based on the distribution of cerebral involvement or motor signs, such as hemiplegia, quadriplegia or diplegia.

Although CP is the commonest cause of motor disability in childhood, in many cases the exact aetiology remains difficult to be ascertained accurately. The more common causes for CP are tabulated in Table 1, and these can be divided based on the timing of the cerebral damage or insult, i.e. prenatal, perinatal or postnatal.

Of importance is the recognition that the risk of CP is strongly associated with the gestational age with preterm infants accounting for 25% of all patients with CP in Sweden⁴. The risk of CP among every preterm children is approximately one in 20 survivors, compared to the risk of less than one per 1000

Table 1: Common causes of cerebral palsy**Prenatal**

- Cerebral malformation syndromes
 - agenesis of corpus callosum
 - pachygyria-agyria
 - schizencephaly
 - Dandy-Walker malformation (of the cerebellum)

Maternal deficiencies

- chronic maternal abuses (alcohol, drugs)
- intra-uterine infections (ToRCH complex)

Intra-uterine / foetal stroke

- inherited thrombophilic tendency
- placental abnormalities
 - a) foetal vasculopathy
 - b) chorioamnionitis
 - c) placental vascular necrosis

Perinatal

Birth asphyxia (hypoxic-ischemic encephalopathy)

- term infants
- pre-term (low birth weight) babies

Periventricular hemorrhagic infarction

Postnatal

Central nervous system infection

- meningitis
- encephalitis

Traumatic head injury

Shaken baby syndrome

Progressive hydrocephalus (non shunted cases with expanding heads)

Strokes

- thrombophilic tendency
 - a) anti-phospholipid antibody
 - b) factor V Leiden mutation

survivors in children weighing more than 2500g at birth. This is because in preterm babies, the periventricular watershed areas are fragile and particularly vulnerable to ischemia from mild or transient disturbance in blood pressure that often escapes detection, even by careful monitoring. In preterm babies who develop CP, about two thirds are characterised by the spastic diplegic or ataxic-diplegia type, following periventricular leukomalacia or periventricular haemorrhagic infarction.

The role of infection and/or inflammation in the aetiology of preterm birth has gained prominence in recent years. Preterm infants had higher rates of exposure to ascending intra-uterine infections. This impression is supported by the frequent findings of positive cultures for infection in preterm CP, as compared to only rare associations with cord blood metabolic acidosis⁵. Studies measuring the inflammatory cytokines in the amniotic fluid showed that these were raised in foetuses that were born preterm⁶. When compared to matched controls, children with CP had more variants of single nucleotide polymorphisms in proteins associated with nitric oxide production, thrombosis, hypertension and inflammation⁷. All these data lend credence to the CP hypothesis by Kendall and Pebbles⁸, who put forward a stepwise pathway of sensitisation followed by injury. Thus, mild hypoxia may be damaging if the foetus' compensatory mechanisms have been down regulated or overwhelmed by another inflammatory insult.

Against widely held assumptions, obstetric complications that can interrupt the supply of oxygen in term infants are rare in survivors and this do not account for most cases of CP. Of these complications, only tight nuchal cord⁹ accounted for 6% of spastic quadriplegic CP. In most term infants who had birth asphyxia, there are often additional risk factors such as intra-uterine exposure to infection or coagulation disorders¹⁰, suggesting that more than a single risk factor may often be required to result in an adverse outcome. Similar to preterm babies, markers of maternal infection were associated with an estimated nine fold increase risk of spastic CP¹¹. Most of these infants did not have recognised infections in the newborn period. However, exposure to intra-uterine infection was associated with meconium aspiration syndrome, low APGAR scores and the need for resuscitation, i.e. features that are often mistaken for asphyxia during birth.

Perinatally acquired stroke occurs one in 4,000 pregnancies. This contributes towards a portion of hemiplegic CP and some spastic quadriplegic CP. Almost two-thirds of infants with porencephaly or ischemic stroke had at least one prothrombotic abnormality in their blood¹². Preterm infants who were homozygous or heterozygous for mutation of the enzyme methylene-tetrahydrofolate reductase had a significantly increased risk of developing diplegia¹³. Amongst the many prothrombotic disorders, the presence of anti-cardiolipin antibody was the most frequent prothrombotic factor identified in a group of infants with cerebral thromboembolism¹⁴. Besides anti-phospholipid antibodies, cerebral thromboembolism was reported to be associated with the factor V Leiden mutation¹⁵, the most common genetic thrombophilia. By itself, the Leiden mutation results in only a low risk of thrombosis, but the addition of other genetic or acquired factors increases the risk sharply. The thrombophilic tendency is often one of the contributory factors to other risk factors such as nulliparity, subfertility, pre-eclampsia, emergency Caesarean section, vacuum delivery, prolonged rupture of membranes and cord abnormalities, with 60% of patients having three or more of these risk factors¹⁶. Abnormalities of the placenta and its vasculature may predispose to thromboses that may then embolise into the foetal circulation, and reach the cerebral circulation via the patent foramen ovale. When placentas were examined in children with CP, the most common histopathological lesion identified were thrombotic lesions. In some patients, these placental abnormalities were also associated with presence of anti-phospholipid antibodies¹⁷ and the factor V Leiden mutation¹⁸.

PAEDIATRIC NEUROMUSCULAR DISEASES

Physical disability in a child may result following an acute illness affecting the lower motor neuron, an example of which is Guillain-Barré syndrome (post-infectious or post-inflammatory ascending polyradiculopathy). Another example would be neuromuscular weakness resulting from a spinal lesion, which can present acutely following traumatic spinal

injury or infectious transverse myelitis, or present subacutely following an expanding spinal tumour or metastasis.

Most of the children with neuromuscular disorders present with inability to walk since birth or with progressive muscle weakness that results ultimately in inability to walk. The first group includes the more severe forms of spinal muscular atrophy (SMA). In infants with type I SMA or Werdnig-Hoffman disease, the hypotonia is so marked that the infant will not be able to sit up at all before demise in infancy or early childhood. In children with the intermediate form of SMA, i.e. type II SMA, they are able to sit but not walk. Thus, they benefit immensely from the use of motorised wheelchair. With progression of the disease where there is shortened survival of the spinal motor neuron, the weakness results in gradual inability to sit. Respiratory support is then needed to prolong their lifespan. SMA is a disease showing autosomal recessive inheritance with an incidence of 1 per 6,000 - 8,000 live births¹⁹. The genes that are thought to be involved in SMA include the survival motor neuron (SMN) gene and the neuronal apoptosis inhibitory protein (NAIP) gene, both of which were mapped to chromosome 5q11.2-13.3. The NAIP gene is thought to play a role in modifying the disease severity²⁰ and provides an explanation for the different clinical phenotypes.

The most common progressive neuromuscular disorder is Duchenne muscular dystrophy (DMD), which affects 1 per 3,500 male births. It is caused by mutations in the dystrophin gene²¹. Dystrophin is a very important protein found in skeletal muscles and its absence renders the sarcolemma fragile, making the muscle fibres susceptible to excessive degeneration with use. In this condition, the boys will be able to achieve independent ambulation although there may be a mild delay in their milestones for walking. The clue to the condition lies in the difficulty for them to climb up steps and later, difficulty getting up from a seated position without the need to push up with their upper limbs. The diagnosis is supported by the presence of markedly elevated serum creatine kinase levels, often reaching 10,000 U/L. With a typical clinical picture and the raised serum creatine kinase, 50% of the patients can have their diagnosis confirmed using blood test for the common genetic mutations (deletions and duplications) resulting in DMD. In the other 50% of patients, a muscle biopsy is required to confirm the diagnosis when there is absence (or less than 10%) of dystrophin in the muscle fibres. There is recent evidence from randomised controlled trials that corticosteroid therapy for DMD improves muscle strength and function in the short term with benefit lasting 6 months to 2 years²². In addition, there is also some evidence to suggest that deflazacort, which is a steroid with lesser side effects such as weight gain, may help preserve the left ventricular²³ and pulmonary²⁴ function in DMD. Presently, the most optimal dose of prednisolone is 0.75 mg/kg/day. Nevertheless, there continues to be concern on the adverse effects from long term steroid use, and alternative dosage regimens, such as using intermittent low-dose prednisolone, are being studied²⁵. When no longer ambulant, a motorised wheelchair

will allow them to carry on with most of the activities of daily living, in particular, continuing on in school and tertiary education. These patients are encouraged to use the incentive spirometry to maintain their respiratory efforts for as long as possible. A well-fitted wheelchair will slow down the onset of scoliosis, which will further adversely affect their respiratory function. Becker muscular dystrophy, the milder allelic variant, is less common at 1 in 18,500 live births, and tends to have a later onset and a less severe course.

Besides X-linked muscular dystrophy, the limb girdle muscular dystrophies (LGMD) are a group of diseases with progressive, symmetric, proximal muscle weakness with variable onset of presentation, from early childhood to the second decade of life²⁶. The current classification is based on the mode of inheritance and the order in which they are discovered. Type I LGMD have autosomal dominant inheritance, whereas type II LGMD have autosomal recessive inheritance. These patients share many clinical similarities, together with increased myopathic changes on electromyography and signs of muscle fibre degeneration and regeneration on the muscle biopsy. The abnormal gene products had been identified in many of the LGMD. These include proteins assisting the dystrophin in anchoring the muscle cytoskeleton to the extracellular matrix, e.g. proteins making up the sarcoglycan complex. Some of the proteins are instead involved in sarcolemmal signal transduction, e.g. calpain-3 and dysferlin.

Next are the congenital muscular dystrophies (CMD), which is a heterogeneous group of neuromuscular diseases that present in infancy. The typical features are early, usually infantile, hypotonia and motor delay. Creatine kinase may be normal or raised and the muscle biopsies show typical dystrophic changes. The CMD are classified based on the presence or absence of merosin, a protein in the basal lamina of skeletal muscle fibres that links the dystrophin-associated proteins to the extra-cellular matrix. Thus, the merosin-negative CMD are more severe than the merosin-positive CMD²⁷. The merosin-deficient CMD are characterised by more severe hypotonia and contractures. They are accompanied by variable degrees of central (cerebral) hypomyelination²⁸ seen on neuroimaging, and sometimes slowing of nerve conduction velocity²⁹ that indicate a peripheral neuropathy as well. A third group of CMD shows frank structural brain abnormalities, such as neuronal migration defects³⁰, which are not just the hypomyelination described above. This group includes Fukuyama CMD, muscle-eye-brain disease (Santovuori syndrome) and Walker-Warburg syndrome.

Lastly is the group of congenital (structural) myopathies that presents at birth or in infancy with hypotonia, muscle weakness and motor delay. The classification is based on the electron microscopy findings of the muscle fibres. The more common types include nemaline myopathy, central core disease, myotubular (centronuclear) myopathy, congenital fibre type disproportion and mitochondrial myopathy. Most of these are fairly mild and are often non-progressive or only very slowly progressive (as opposed to the muscular dystrophies). These

can be inherited in an autosomal dominant or recessive fashion, with sex-linked form of myotubular myopathy reported as well. Mitochondrial myopathy can present with muscle weakness or often muscle cramp/pain after exercise, and may be associated with lactic acidosis. Other high energy utilisation organ, such as the brain, kidneys and liver, may also be affected. The difference in phenotypic expression and severity is due to the number and distribution of the defective mitochondrial genes in the different organ system in different individuals.

SPINA BIFIDA (MYELOMENINGOCELE)

Spina bifida (myelomeningocele) results from failure of fusion of the caudal neural tube by the 28th day post-conception. The cause for this disorder is heterogeneous and includes chromosomal abnormalities, single gene disorders and teratogenic exposures³¹. Nevertheless, the cause is not known in most cases and the affected individuals do not have an underlying malformation syndrome. However, the risk of spina bifida or anencephaly, or both, in siblings of affected individuals ranges from 3% to 8%, and is consistently higher than that of the general population³². This underlines the importance of the findings from the Medical Research Council Vitamin Study Research Group, which showed from a multi-centre randomised control trial that maternal peri-conceptual folic acid supplementation provided a 72% protective effect (relative risk ratio 0.28) when compared to controls³³. Similar results were also obtained from case-controls studies and community interventions. These showed that the lack of folic acid supplementation prior to conception increases the risk of having an affected child by two to eight fold³⁴. Based on these studies, the recommended folic acid intakes are 4 mg/day for those women at high risk (a previous pregnancy with neural tube defect) and at least 0.4 mg/day for all other women who are capable of becoming pregnant³⁵. Besides folic acid, there is also evidence to support a moderate association between low maternal vitamin B12 concentrations and higher risk of neural tube defects (relative risk of 3)³⁶.

The severity of the physical disability depends to a large extent on the neurosegmental (functional) level of the spinal lesion. This usually corresponds to the anatomical level of the bony spinal defect as determined by the neuroimaging studies. The neurological deficits result in weakness or paralysis of the lower limb muscles, sensory loss, bladder and bowel dysfunction, and orthopaedic deformities such as clubfoot, hip dislocation, and kyphoscoliosis. Most children with lower lumbar involvement are able to achieve independent walking with the use of ankle brace. With a high lumbar lesion, the children can often walk using elbow crutches with orthotic appliance for the lower limbs. If it is a thoracic level lesion, it becomes increasingly difficult for the child to ambulate even with aids, and the wheelchair maybe the only realistic option. Besides the physical disability and other complications, individuals with spina bifida are also at risk for central nervous system malformations such as hydrocephalus and Chiari II malformations. The need for shunting increases with the level of the lesion, i.e. most with

thoracic lesion required a shunt, whereas less than 70% with a sacral lesion required a shunt³⁷. Although most have normal intelligence, language difficulties are more common in children with spina bifida³⁸ and this may affect their ability to be independent and economically productive in future.

CONDITIONS WITH MENTAL DISABILITY IN INFANTS AND CHILDREN

Mental Retardation

Most of the children who are confirmed subsequently to have mental retardation using standardised tests of intelligence and adaptive behaviour, already presented with global developmental delay in infancy and early childhood. The areas affected are predominantly in the domains of speech/language, cognition, personal/social skills (including play) and activities of daily living. Mental retardation affects approximately 1% of school-aged children but the diagnosis for the cause of the mental retardation is established in only 30 to 50% of the cases³⁹. This is despite a detailed clinical history assessing the pregnancy, perinatal history, family history and social history, as well as a careful examination looking for signs of dysmorphic features and congenital anomalies.

Mental disability could be caused by any condition that impairs the development of the brain before birth, during birth or in the childhood years. The conditions resulting in mental retardation range from congenital dysmorphic syndromes to poverty, malnutrition and maternal education (Table 2). The adverse effect of poor nutrition in early life on cognition is evident with protein-energy malnutrition, iron deficiency in infancy, iodine and vitamin B12 deficiency in childhood. There is a strong inverse relationship between maternal education and prevalence of mental retardation in children without other neurologic conditions⁴⁰. Based on the more common causes listed, some specialised laboratory investigations are required to help ascertain the aetiology. These include cytogenetic analysis for chromosomal abnormalities especially when there are dysmorphic features or family history of mental retardation. After Down syndrome, the next most common genetic cause for mental retardation in boys is fragile X syndrome. Screening for metabolic disorders will provide a higher yield in the presence of parental consanguinity, multiple organ involvement and developmental regression. Magnetic resonance imaging of the brain is more likely to yield a positive result when there are asymmetric neurological findings or abnormal head size.

Establishing a diagnosis for the mental retardation is helpful for prognostication and genetic counselling for future pregnancies. For some neurometabolic diseases, specific therapeutic interventions may be possible e.g. dietary treatment for phenylketonuria. Even if no diagnosis is ascertained immediately, it may become apparent with time in particular, the dysmorphic syndromes. Based on the clinical progress, further specialised tests can be performed or repeated when the need arises.

Table 2: Common causes of mental retardation**Prenatal**

- Genetic syndromes
 - Down syndrome
 - Fragile X syndrome
 - Prader-Willi syndrome and Angelman syndrome

Inborn errors of metabolism

- Phenylketonuria
- Organic aciduria (maple syrup urine disease)

Cerebral malformation syndromes

Maternal deficiencies

- Foetal alcohol syndrome
- Drug abuse (cocaine)
- Intra-uterine infections (ToRCH complex)

Perinatal

- Birth asphyxia
- Hypoxic state in premature delivery

Postnatal

- Central nervous system infection
 - Meningitis
 - Encephalitis
- Traumatic head injury
- Progressive hydrocephalus (non shunted cases with expanding heads)
- Environmental toxins
 - Lead
 - Mercury
- Malnutrition
 - Protein-energy malnutrition
 - Mineral and vitamin deficiencies
- Poverty and social deprivation
- Maternal education

Autistic Spectrum Disorder

Autistic spectrum disorder (ASD) refers to a disorder of the nervous system that affects the way the brain develops and functions, with onset before 3 years of age. The disorder is characterised by problems with verbal and non-verbal (e.g. gestures and facial expressions) communications, social interactions, usually limited interests and activities, and obsession with routine and order. Often there are some classic repetitive behaviour such as opening/closing doors, flipping light switches, water play and paper shredding. There may also be some motor stereotypes such as hand flapping, body rocking, finger-flicking and self-spinning. Although quite simply defined, the presentation can be extremely variable. This clinical nature, together with the lack of well-defined diagnostic tool or a definitive biologic marker or test, contributes to the delay in the diagnosis for many⁴¹. Although not part of the diagnostic criteria, abnormal responses to various sensory inputs, including auditory, visual, and tactile stimuli, are often also seen in the affected children⁴².

In ASD, the children do not always exhibit the same symptoms, and the symptoms also depend on the severity of the disorder. In addition, there are differential diagnoses for autistic behaviours that need to be considered before ascertaining the diagnosis for ASD. The more common amongst these are severe or profound mental retardation and psychiatric conditions

such as childhood schizophrenia, bipolar disorders, severe neglect or abuse. The more common neurological disorders with autistic features include fragile X⁴³, and tuberous sclerosis⁴⁴ especially when there is associated malignant epileptic encephalopathy such as West syndrome and Lennox-Gastaut syndrome. Other genetic conditions with significant autistic features include Rett syndrome (mutation in MeCP2 gene) and Angelman syndrome (duplication of chromosome 15q). Generally, it is easy to exclude neurodegenerative disorders with cognitive deterioration and autistic features from ASD because of the absence of the expected ASD clinical feature before the onset of the decline. However, there were some reports indicating that up to a third of children with ASD were noted to have unexplained regression of language and social skills, usually between the age of 18 and 24 months⁴⁵. Thus, specific testing to exclude inborn errors of metabolism may be required in the presence of clinical indications.

Although there is no medical treatment for ASD, many of the co-morbid symptoms such as obsessive compulsive behaviour, aggression and hyperactivity, and sleep disturbance can be managed and treated accordingly. Clearly, there is now a greater need for early diagnosis of ASD as better cognitive and behavioural outcome is possible with early intervention programmes, and in particular, the use of intensive applied behavioural treatment starting as early as 4 years of age². Parental education and support together with the early intervention strategies in the community can help children with ASD maximise their developmental potential.

STRATEGIES TO PREVENT OR REDUCE PHYSICAL AND/OR MENTAL DISABILITIES IN INFANTS AND CHILDREN**A) Before Pregnancy**

- 1) Genetic counselling
 - a) history of an affected child with suspected genetic/chromosomal disorder
 - b) history of two or more miscarriages or a baby who died in infancy
 - c) mother is 35 years of age or more
 - d) consanguineous parents
- 2) Avoid alcohol, illegal drugs, and smoking
- 3) Proper balanced diet and vitamin supplementation, including folic acid
- 4) Review the medication(s) that woman is on
- 5) Updating immunisations (e.g. rubella if not previously done)

B) During Pregnancy

- 1) Early prenatal care and follow-up
- 2) Adequate rest and sleep
- 3) Nutrition meals

C) Prematurity and Low Birth Weight Baby

D) Newborn

- 1) Screening
 - a) congenital hypothyroidism
 - b) inborn errors of metabolism

E) Infancy

- 1) Vaccination against
 - a) measles and rubella
 - b) hemophilus influenza
 - c) invasive pneumococcal disease

F) Childhood

- 1) Preventive measures against traumatic brain injury
 - a) safety seat (child car seat) and safety belt when travelling in a car
 - b) use of bicycle helmets
 - c) water safety against drowning or near-drowning
 - d) home safety to prevent accidental falls
- 2) Reduce exposure to environmental toxins that result in brain damage
 - a) lead
 - b) mercury
- 3) Reduce poverty and social deprivation
- 4) Emphasise the need for a balanced diet

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LEARNING POINTS

- o Disability in children can be broadly classified into physical and mental disabilities.
 - o Physical disability is often present in children with cerebral palsy or neuromuscular disorders. With mental disability, the children are not able to learn self help skills and remain dependent on their caregivers for most of the activities of daily living.
 - o Mentally disabled children include those with moderate to severe autism.
 - o In paediatrics, many conditions result in both physical and mental disabilities, with greater consequence and burden to their families.
 - o Long term care and rehabilitation remains the most challenging task for all involved in the care of disabled children.
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