<running head> Symposium: Cerebral Palsy

THE MEDICAL MANAGEMENT OF CEREBRAL PALSY

Martin Smith PhD FRCPCH is a Consultant Paediatric Neurologist based in John Radcliffe Hospital, Oxford, UK

Manju A Kurian MA, MRCPCH, PhD is a Clinician Scientist in Paediatric Neuroscience with the Neurosciences Unit, UCL – Institute of Child Health, London, UK

Abstract

Medical management of cerebral palsy is a complex issue that should be undertaken with the overall aim to improve comfort, function in every day life, self confidence, participation and independence.

Although the main focus is commonly the motor disorder, medical management also encompasses far wider issues including the management of multiple co-morbidities (e.g. epilepsy, visual and hearing impairment, gastro-oesophageal reflux and constipation, learning and behavioural difficulties) which require close multi-disciplinary teamwork.

High muscle tone can be broadly considered as either spasticity, dystonia, or commonly a mixed pattern. Strategies to reduce muscle tone include enteral medication, Botulinum neurotoxin, intra-thecal Baclofen, and selective dorsal rhizotomy. However, strength training and reduction of inserted involuntary movements are equally important strategies to improve function.

We also discuss treatable conditions which mimic cerebral palsy, and explore potential future therapies such as stem cells.

Keywords

Cerebral Palsy

Spasticity

Dystonia

Personal practice points:

- All children with a new diagnosis of cerebral palsy should undergo brain imaging, ideally MRI scan
- Although up to 20% of scans can be normal, this should prompt investigation for alternative causes, several of which can be treatable (including dopa responsive dystonia and GLUT 1 deficiency)
- Invasive tone reduction therapies (e.g. botulinum neurotoxin, intra-thecal baclofen and selective dorsal rhizotomy) are increasingly available but should only be undertaken following detailed multi-disciplinary assessment and careful negotiation of goals and expectations with the child and family

Introduction (level A heading)

Cerebral palsy is a disorder of abnormal tone and posture arising from a non-progressive abnormality of the infant brain. The majority of affected individuals will have increased muscle tone, although in a small minority tone may be normal or reduced. Variants of ataxic and hypotonic cerebral palsy are still recognised, although long term vigilance for progressive neurological disease is particularly important in these cases.

Two main types of hypertonicity are recognised, i.e. spasticity and dystonia, although the two commonly co-exist. Both involve co-contraction of agonist and antagonistic muscle groups, but differ in important ways. Spasticity is defined as a velocity dependent increase in muscle tone, which leads to clinical signs including a spastic "catch", clonus and brisk deep tendon jerk reflexes. Dystonia is more fluctuant, not velocity dependent, and more likely to lead to twisting postures.

The majority of currently available medical therapies are directed at tone reduction, but it is vital to emphasise that hypertonicity is just one aspect of the upper motor neuron syndrome, and that in many children the other associated features of poor motor control or weakness are a greater barrier to function. Great care must be exercised in strategies to reduce muscle tone (particularly in irreversible procedures such as selective dorsal rhizotomy), as some children are reliant on spasticity to functionally compensate for major underlying weakness. In this situation spasticity reduction can lead to an unwelcome reduction in functional performance.

Strategies to improve function, reduce pain, and therefore improve quality of life in young people with cerebral palsy can include:

- Tone reduction to reduce contractures, postural deformity, and discomfort
- Strength training to improve weakness
- Improve co-ordination by better motor control or reduction of involuntary inserted movements

It is vital to emphasise that medical management should always be in the context of input from a multi-disciplinary team. For example, tone reduction without

physiotherapy is almost always futile. The above strategies must also be placed within the wider context of management of the associated co-morbidities of cerebral palsy, which commonly include complex multi-organ pathology (see table 1).

INSERT TABLE 1

Assessment (A)

Before undertaking any interventions it is essential to perform a detailed baseline physical assessment, including:

- Assessment of tone – the modified Ashworth score is a useful tool to quantify the degree of spasticity in individual muscles. In subjects with predominant dystonia this can be quantified with tools such as the Burke-Fahn-Marsden, Barry-Albright or Dyskinesia Rating Scale. Where spasticity and dystonia appear to co-exist the Hypertonia Assessment Scale can be considered.
- Careful documentation of fixed contractures (sometimes examination under anaesthetic is very helpful)
- Assessment of power (e.g. using the MRC 5 point scale)
- Documentation of functional levels. If time permits the gross motor function measure (GMFM) is a well validated detailed assessment tool able to demonstrate even relatively small changes in function. In a busy clinic the gross motor function classification score (GMFCS) is a quick and useful guide to level of mobility, as is the manual ability classification score (MACS) for upper limb function. Gait analysis where available is very helpful, and should be strongly considered if orthopaedic or neurosurgery is contemplated.

Neurological Investigations (A)

Imaging of the brain should be performed in all suspected cases of cerebral palsy. Rarely a space occupying lesion will be discovered that requires urgent neurosurgical assessment (e.g. a brain tumour, or arachnoid cyst obstructing CSF flow causing hydrocephalus). Although as many as 20% of children with cerebral palsy are known to have normal imaging, it should nevertheless raise clinical suspicion of the possibility of an alternative diagnosis, some of which are treatable, including:

- Tethered spinal cord
- Segawa syndrome (also known as dopa-responsive dystonia). Although rare this is an important condition not to miss as the motor symptoms are fully reversible with low dose L-dopa.
- GLUT1 deficiency. This is a disorder of brain energy metabolism due to impaired glucose transport into the brain. It can present with seizures, persistent/paroxysmal movement disorders, gait abnormalities and motor developmental delay. Diagnosis can be achieved by either demonstration of a low CSF to plasma glucose concentration (typically less than 0.4, although higher ratios are reported) and mutation analysis of the *SLC2A1* gene. The ketogenic diet can be helpful in both epilepsy and movement disorders due to GLUT1 deficiency.
- Metabolic disease including glutaric aciduria type 1, biotinidase deficiency, mitochondrial disease
- Single gene disorders such as hereditary spastic paraparesis (although onset is only rarely in infancy)

Conventional medical therapies to reduce hypertonicity (A)

Conventional medical therapies to reduce spasticity and/or dystonia can be targeted in 4 main ways:

1. Direct muscle relaxants
2. Denervation or neuromuscular blockade
3. Central inhibition
4. Reduction of afferent input from the hypersensitive stretch reflex by selective dorsal rhizotomy

Alternatively they can be considered via their route of administration e.g. enteral medications (see table 2), localised injections (e.g. botulinum neurotoxin), or more general measures (e.g. intra-thecal baclofen or selective dorsal rhizotomy).

1. Direct muscle relaxants (level B heading)

Dantrolene inhibits calcium release from the sarcoplasmic reticulum of muscle cells. Although generally safe, there are reports of dantrolene associated hepatitis in adults, and therefore it is recommended that liver function tests are monitored prior to and at intervals after starting therapy.

2. Denervation or neuromuscular blockade (B)

Chemical denervation can be achieved using either Botulinum neurotoxin (BoNT) or Phenol. BoNT has been in widespread use for over 20 years. In addition to tone reduction, it is also used in cerebral palsy to reduce drooling and correction of strabismus.

The majority of medical use is type A toxin (BoNT-A), which is composed of a heavy and light chain. The light chain interferes with the binding and release of acetylcholine across the muscle junction, thereby resulting in weakness due to

chemical denervation. The effect usually lasts 3-4 months, until reinnervation occurs due to progressive nerve sprouting.

The two major drawbacks to BoNT-A are the short term duration of effect, and the need for it to be administered by injection, usually into multiple muscle groups. The majority of injections for children in the UK are performed under sedation (e.g. Midazolam), or with inhaled nitrous oxide. General anaesthesia still has a role, and has the additional advantage of allowing a detailed assessment of fixed contractures. Most experts agree on the need for accurate localisation of the muscle. Large muscles (e.g. gatrocnemius) can usually be safely identified on anatomical grounds, but injection of small or deep seated muscles is aided by nerve stimulator or ultrasound guidance. Some experts also stress the need to inject as near to the motor end plate as possible, although others argue that the inevitable diffusion throughout the injected (and adjacent) muscles renders this non-essential.

There are several different commercially available preparations of BoNT-A available in the UK. Differences are claimed by the manufacturers in relation to the degree of protein binding (which may affect the extent of diffusion to adjacent or more widespread muscle groups), but the main thing to highlight to the novice is that the dosage in units per kg varies between the two most widely used products (Botox® and Dysport®). A precise comparison is not published, but as a general guide most clinicians consider a ratio of between 2-3 units of Dysport® to 1 unit of Botox®.

Theoretical concerns about BoNT-A include the long term effect on muscle architecture, and there is some data derived from animal experiments demonstrating the potential for retrograde transmission into the CNS. However, the safety record of BoNT-A in clinical practice is remarkably good, although transient unwanted effects are not uncommon (e.g. pain at injection site, flu like symptoms, weakness). The more serious side effects include an association with dysphagia (more likely after head or neck injections), and a small increase in chest infections. The more serious side effects are more common in children with the greatest degree of physical impairment, and when higher doses are used. As a consequence many clinicians are now cautious in using very high doses in severe neurodisability.

There are now a large number of publications demonstrating relatively short term reduction in muscle tone leading to increased range of joint movement and/or

improved ambulation, but very limited data on long term benefits in gait or upper limb function.

3. Central inhibition (B)

Enteral administered medication (level C heading)

Enteral therapies to reduce muscle tone due to spasticity and/or dystonia by central inhibition are summarised in table 2.

INSERT TABLE 2

Baclofen is an agonist of GABA, an inhibitory neurotransmitter, with purported effect at both spinal interneurons and within the brain. Double blind trials have shown clear evidence of spasticity reduction in adults, although benefit is often modest from oral use and unwanted effects common. These can include fatigue, drowsiness, or loss of function due to weakness e.g. loss of head control.

Diazepam is believed to have muscle relaxant and a central inhibitory effect on muscle tone, via GABA-A receptors. It also has an anxiolytic effect. Sedation is a concern, although provided it is started at a low dose and increased gradually serious short term side effects are uncommon. There are however concerns about long term dependency in adults. Diazepam is therefore best used for short courses, or in children with a significantly reduced life expectancy who experience frequent distressing symptoms. If withdrawn after long term use it should always be weaned over a prolonged period of many months.

Tizanidine acts centrally via alpha-2 adrenergic receptors. It is licensed for use in adults with multiple sclerosis, but can be used in children with caution. Monitoring of liver function is necessary.

Gabapentin was initially developed for use in epilepsy, but is also effective in neuropathic pain, and there are case reports of benefit in spasticity reduction.

Trihexiphenidyl is an anti-cholinergic therapy that is often effective in both primary and secondary dystonia. It has little effect on spasticity. The mechanism of action is believed to be central. Side effects are predictable and dose related, including dry mouth, constipation, urinary retention, and blurred vision. They are reversible on discontinuing medication.

L-dopa (L-3,4-dihydroxyphenylalanine) is the precursor of the neurotransmitter dopamine is the amino acid precursor of dopamine. Doses of L-dopa as low as 0.5mg/kg three times daily are sufficient to produce a dramatic response in Segawa syndrome, although other neurotransmitter disorders (e.g. the pterin defects and tyrosine hydroxylase deficiency) may require higher doses of between 3 and 10 mg/kg three times daily. Response in secondary dystonia is often minimal and therefore L-dopa is often used only for short term trials unless there is a striking improvement. L-dopa is given in a combined preparation with a peripheral dopa-decarboxylase inhibitor which reduces the systemic side effects, commonly nausea, vomiting or postural hypotension. Domperidone can also be used if nausea is particularly problematic. Rarely L-dopa will exacerbate dyskinetic movements.

Intra-thecal Baclofen (ITB) (C)

Although Baclofen is rapidly absorbed following oral administration it has relatively poor lipid solubility and only limited penetration into the central nervous system. Efficacy is dramatically improved by intra-thecal (or intra-ventricular) delivery which bypasses the blood brain barrier. Doses used are typically less than 1% of the enteral equivalent, often between 200 to 800 micrograms per day. Most commonly this is delivered at a continuous steady rate which can be adjusted by an external programmer.

The clear indication for ITB is in non-ambulant children with severe spasticity. This has been shown to improve comfort and ease of care. Intuitively it might also be expected to reduce the rate of hip migration although this is not yet confirmed. The effect on progression of scoliosis is more unpredictable. ITB is also potentially attractive in ambulant children as an alternative to selective dorsal rhizotomy. It has the advantages of being reversible, and titratable, and would therefore be more

appropriate in children with progressive illnesses, significant co-existent dystonia, and those in whom there is concern about underlying weakness. However, current experience in ambulant children is limited and inconclusive.

Pre-surgical evaluation should always include a detailed assessment as above, and in most centres a test dose in strongly recommended. Although rare, there do appear a small minority (approximately 5%) of non-responders to a test dose in whom proceeding to implantation will be at best disappointing. The test dose is commonly delivered as a single intra-thecal bolus of 50 micrograms, followed by careful medical and physiotherapy assessment at around 4 hours later. Some centres insert a temporary catheter to allow titrated infusions over several days, which may be helpful particularly in secondary dystonia where a delayed effect and higher dose requirements are expected. Opinion is divided between implanting surgeons on the optimal position for the catheter tip. A more rostral position may give more widespread tone reduction, although there is inevitably considerable diffusion throughout the CSF space.

The inevitable down side of ITB pumps is the need for regular refills, typically 3-4 times per year. This involves direct access of the pump via a percutaneous needle. Also in the current generation of pumps the battery tends to last no more than 7 years at which point the entire device needs to be replaced. Reported side effects include infection (occasionally necessitating removal of the device), pump failure (very rare), and catheter disconnection or fracture (not uncommon). The latter two complications can trigger marked rebound spasticity, which can be potentially very serious in a fragile child with complex severe neurodisability. Families should therefore be given a prescription for oral Baclofen to keep in their emergency drug cupboard for this eventuality. Drug overdose can also potentially lead to respiratory impairment.

Deep brain stimulation (A)

Deep brain stimulation (DBS) is increasingly offered to adults with Parkinsons disease, and also widely accepted as first line treatment for primary generalised dystonia in adults and children, many of whom return to normal levels of daily activity. The usual target for electrode placement is bilateral globus pallidus internus.

The benefit in secondary dystonia is less dramatic, but there are small case series and case reports describing benefit in certain sub-groups, including children with pantothenate-kinase associated neurodegeneration (PKAN) and dystonic cerebral palsy following hypoxic-ischaemic injury to the basal ganglia. Further research is required before this can be considered routine practice.

Therapies to improve motor control (A)

Therapies to improve motor control can be considered in two broad groups:

a) Strategies to reduce unwanted (negative) movements

b) Strategies to improve positive features of motor performance (e.g. strength and control)

Enteral medications to reduce unwanted dyskinetic movements include Tetrabenazine, Levetiracetam, Piracetam, Carbamazepine, and Sodium Valproate.

Orthoses have a valuable role to play in motor control and the expert advice of physiotherapists and orthotists is invaluable in obtaining the right prescription. Second skin garments (such as lycra suits) have particular interest in the management of dystonia, as aberrant sensory feedback is a significant contributor to the generation of dystonic movements.

Historically there was a school of thought that discouraged strength training due to concerns that it may exacerbate spasticity. However, there is now good evidence that this anxiety is unfounded, and strength training and exercise has a valuable role in improving function. This can be delivered by exercise programs, and/or in conjunction with functional electrical stimulation.

Unconventional or experimental medical therapies (A)

Many unconventional physical and medical therapies have been offered to children with cerebral palsy. They include special diets, horse riding (hippotherapy) hyperbaric oxygen, and acupuncture, to name but a few. Whilst some of these will almost certainly have additional holistic benefits on quality of life, there is no convincing evidence of functional improvement.

Therapies to encourage or modify brain plasticity (A)

The ability of the developing brain to reorganise (so called brain plasticity) is often quoted as an illustration of the potential for recovery from brain injury by relocation of important cortical functions. Positive examples include the relocation of language skills to the non-dominant hemisphere, and experiments showing that in children born blind the occipital cortex (normally responsible for vision) is integral to Braille reading skills. However, not all brain plasticity is positive and there is some evidence following neonatal stroke that when the unaffected hemisphere develops dominance of control over the paretic limb that this is associated with a poor outcome. The early use (under 12 months) of constraint induced movement therapy in unilateral cerebral palsy to modify brain plasticity remains contentious.

Stem cell transplantation (A)

A common question asked of clinicians working with children with cerebral palsy is whether there is role for stem cells to cure or improve the condition. The use of embryonic human tissue remains highly controversial, but cord blood is another source of embryonic stem cells with far less ethical concerns. Recent advances allowing the transformation of human fibroblasts into induced pluripotent stem cells (and further differentiation into specific types of neurons) are also promising.

In theory the undifferentiated stem cells delivered (by intra-thecal or intra-ventricular injection) into an area of early brain injury might be able to allow regeneration of the injured area. This is intuitively attractive for lesions such as peri-ventricular leucomalacia where the motor cortex may not be directly injured. There is some evidence in murine and primate models this could be feasible, there are several large clinical trials ongoing, and the procedure is now available in China and certain centres in Europe. Nevertheless, at present there is an absence of peer reviewed evidence to support its effectiveness and safety in human subjects, and the authors current practice is to advise caution to parents in this situation.

Case study 1

A 6 year old girl is referred for a second opinion on the diagnosis of cerebral palsy. She was born at term with a normal birth history. Brain MRI is normal. Muscle tone is increased in the lower limbs with brisk reflexes, although downgoing plantar responses. She can walk 10 metres with support, but not unaided. The diagnosis is suggested when her parents ask "why doesn't she have cerebral palsy in the morning doctor?"

Normal brain imaging is compatible with a diagnosis of cerebral palsy, but should always raise concern, particularly if there is an uneventful pregnancy and birth history. Dopa responsive dystonia (Segawa syndrome) is a rare but important mimic of cerebral palsy. It is due to an enzyme deficiency in the generation of tetrahydrobiopterin which is an essential co-factor for the production of Dopamine. Diurnal variation is an important clue, but even when absent clinicians should have a low threshold for an empirical trial of low dose L-dopa. The improvement in usually rapid (within 24 hours) and dramatic. This young lady was walking unaided within a few days, and retains normal mobility at age 16 years. The diagnosis can be confirmed on genetic testing (*GCH1* gene) and/or CSF neurotransmitter analysis.

Case study 2

A 3 year old boy with bilateral lower limb spasticity is referred for evaluation for selective dorsal rhizotomy. He is an ex-premature infant (born at 28 weeks gestation) and his MRI brain scan shows peri-ventricular leucomalacia. He has begun walking with a frame in the last 6 months (GMFCS level III). He has moderate to severe lower limb spasticity, minimal upper limb involvement, and appears strong with good motor control.

He was considered a good candidate for SDR. However, he is still making ongoing functional progress at this age. Reassessment was recommended after age 4 years when he will have begun to plateau in his acquisition of motor skills. In the meantime he continues with 6 monthly Botulinum toxin injections to preserve joint range of movement.

Case study 3

A 10 year old girl is also referred for evaluation for selective dorsal rhizotomy. She developed cerebral palsy as a consequence of group B streptococcal meningitis in the neonatal period. She has severe bilateral spasticity, and is wheelchair dependent (GMFCS level V). She also has severe learning difficulties. Her parents would like her to walk.

After counselling and education of the various options parents accepted SDR was not likely to lead to walking ability. However, they accepted referral for implantation of an intra-thecal Baclofen pump to improve their daughter's comfort and ease of care.

Case study 4

An 8 year old girl with a diagnosis of cerebral palsy is referred for assessment as her condition is worsening. She diagnosed in infancy with hypotonic cerebral palsy walking at age 3 years. However, her gait now appears a combination of spasticity and ataxia.

A diagnosis of GLUT1 deficiency was suspected based on normal brain imaging, and the history of improvement following meals. Fasted CSF to plasma glucose ratio was

0.33, and subsequently a mutation in the *SLC2A1* gene was confirmed. Her symptoms improved on the ketogenic diet.

Conclusion

In the last two decades there have been considerable advances in the medical management of cerebral palsy. The majority of these therapeutic options are currently directed towards tone reduction with the aim to improve range of joint motion, the prevention of postural deformity, improvement of function, and/or improve comfort and ease of care. Function can also be improved by strength training, and strategies to improve motor control.

Further advances, including stem cell therapy, are eagerly awaited although as yet unproven.

Table 1

Associated co-morbidities of cerebral palsy

Neurological	Epilepsy, hydrocephalus, visual and hearing impairment
Behavioural and learning	Sleep disturbance, depression, autistic features, learning difficulties, vulnerability
Gastro-intestinal	Difficulty swallowing, gastro-oesophageal reflux, constipation
Bone	Osteoporosis, scoliosis, hip dislocation, pathological fractures
Respiratory	Susceptibility to chest infections and aspiration
Skin	Drooling, pressure sores
Dental	Poor oral hygiene, susceptibility to dental caries

Table 2

Personal practice of authors for oral medications to treat abnormal tone, posture and inserted movements in children with cerebral palsy

	Spasticity	**Dystonia**	**Dyskinetic movements**
First line	Baclofen	Trihexiphenidyl Gabapentin Clonidine L-dopa (first line if considering Segawa syndrome)	Levetiracetam
Second line	Gabapentin Diazepam	Baclofen Diazepam	Tetrabenazine Sodium Valproate Carbamazepine
Third line	Dantrolene Tizanidine	Carbamazepine (particularly helpful in PKD) Dantrolene	Gabapentin Clonidine Diazepam

Abbreviation:

PKD Paroxysmal kinesogenic dystonia

Further reading

Delgado M R, Hirtz D, Aisen M, et al. Practice parameter: Pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review). *Neurology* 2010; **74:** 336-343

Strobl W, Theologis T, Brunner R, et al. Best clinical practice in botulinum toxin treatment for children with cerebral palsy. Toxins (Basel) 2015; 7(5): 1629-48

Love SC, Novak I, Kentish M, et al. Botulinum toxin assessment, intervention and after-care for lower limb spasticity in children with cerebral palsy: international consensus statement. *Eur J Neurol*. 2010 Aug;17 **Suppl 2**:9-37.

Fehlings D, Novak I, Berweck S, et al. Botulinum toxin assessment, intervention and follow-up for paediatric upper limb hypertonicity: international consensus statement. *Eur J Neurol*. 2010 Aug;17 **Suppl 2**:38-56.

Ng J, Papandreou A, Heales SJ, Kurian MA. Monoamine neurotransmitter disorders-clinical advances and future perspectives. Nat Rev Neurol. 2015 Oct;11(10):567-84.

Faulkner SD, Ruff CA, Fehlings MG. The potential for stem cells in cerebral palsy – piecing together the puzzle. Semin Pediatr Neurol 2013; 20(2): 146-53

Conflict of interest statement

Dr Smith – nil to declare

Dr Kurian is part funded by Action Medical Research. No conflicts of interest to declare.