Botulinum Toxin Service in Cambridge

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Child Development Centre

The talk today

- Botulinum Toxin
- Development of the service
- How the assessments and treatments are managed
- Initial results
- Longer term outcomes
- Future plans

A new treatment for Cerebral Palsy

- Treatment centred around Physiotherapy, orthotic splinting, oral medicine and surgery
- Early 90s reports of treatment of spasticity in children with Botulinum Toxin
- First published studies 1994 showed notable functional improvement
- Relatively rapid service development in tertiary centres

Development of service

- Specialist clinics became rapidly oversubscribed
- Cambridge clinic developed to meet local and regional need in 2000

Botulinum Toxin

- Potent neurotoxin
- Injected locally in spastic muscles
- Targeted anti spastic treatment
- No loss of sensation

Botulinum Toxin A

- Now a widely established clinical treatment of neurological disorders
- Specific licence for Cerebral palsy, but also; Post traumatic brain injury

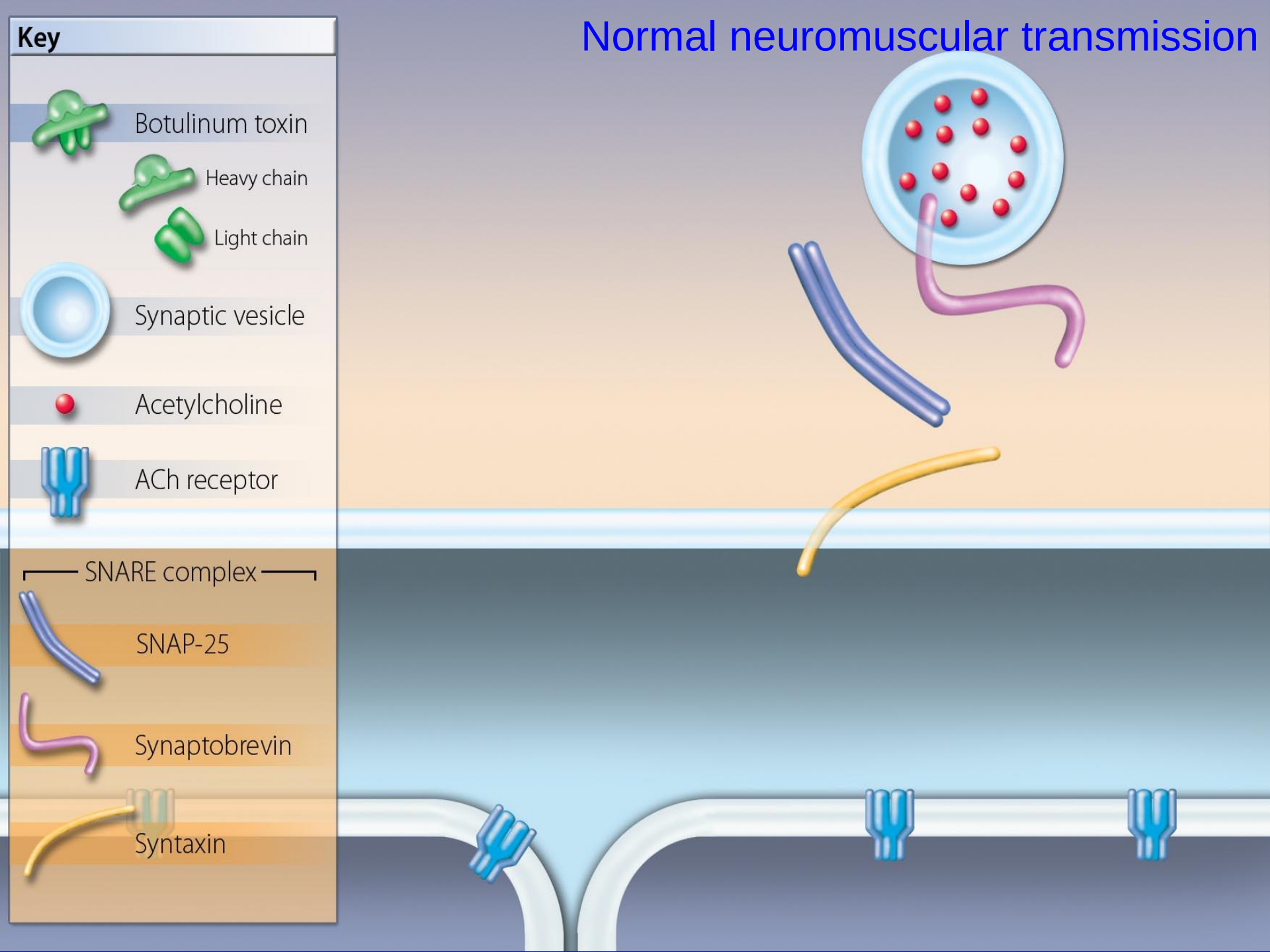
  Genetic conditions

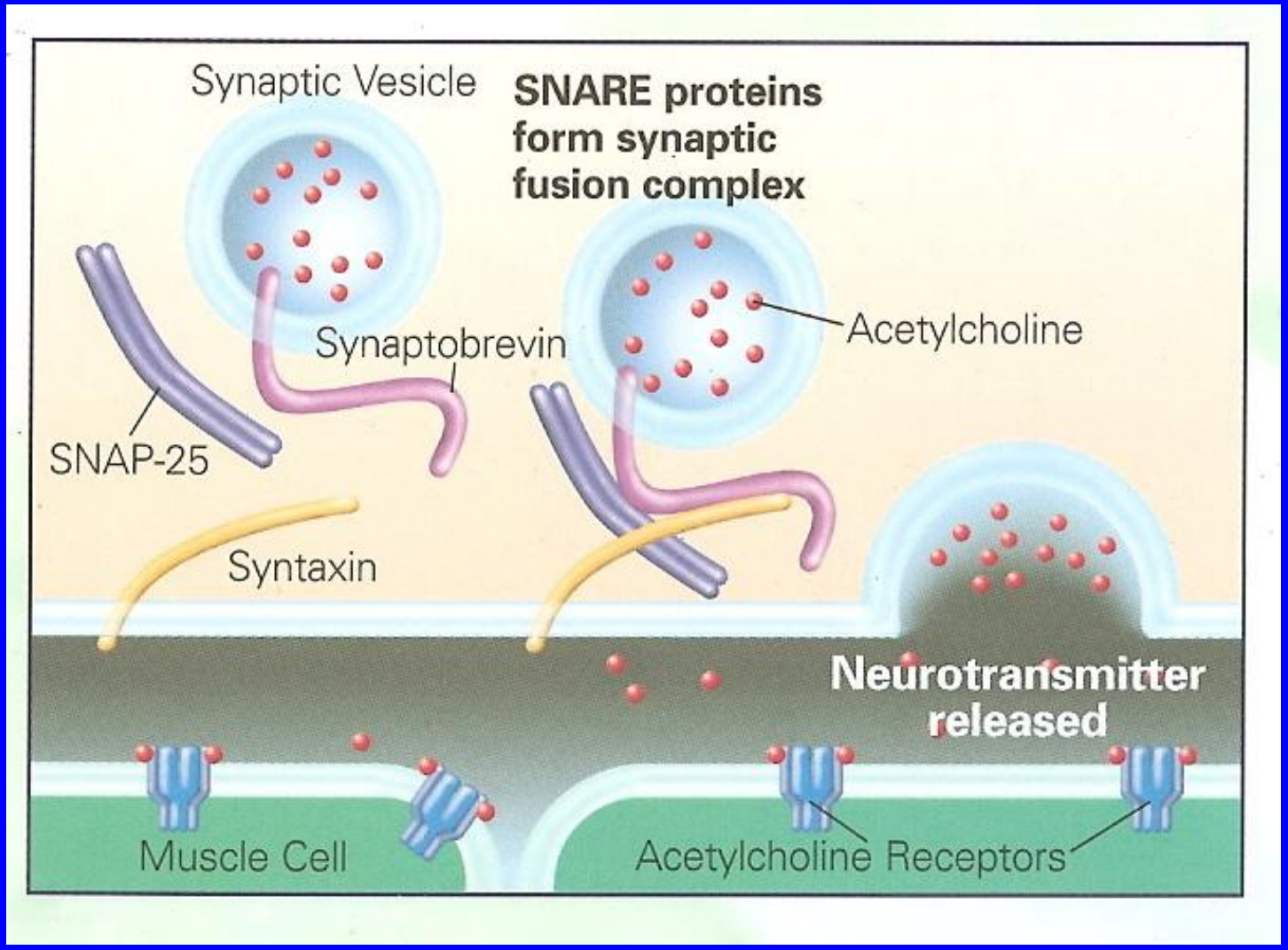
  Metabolic conditions

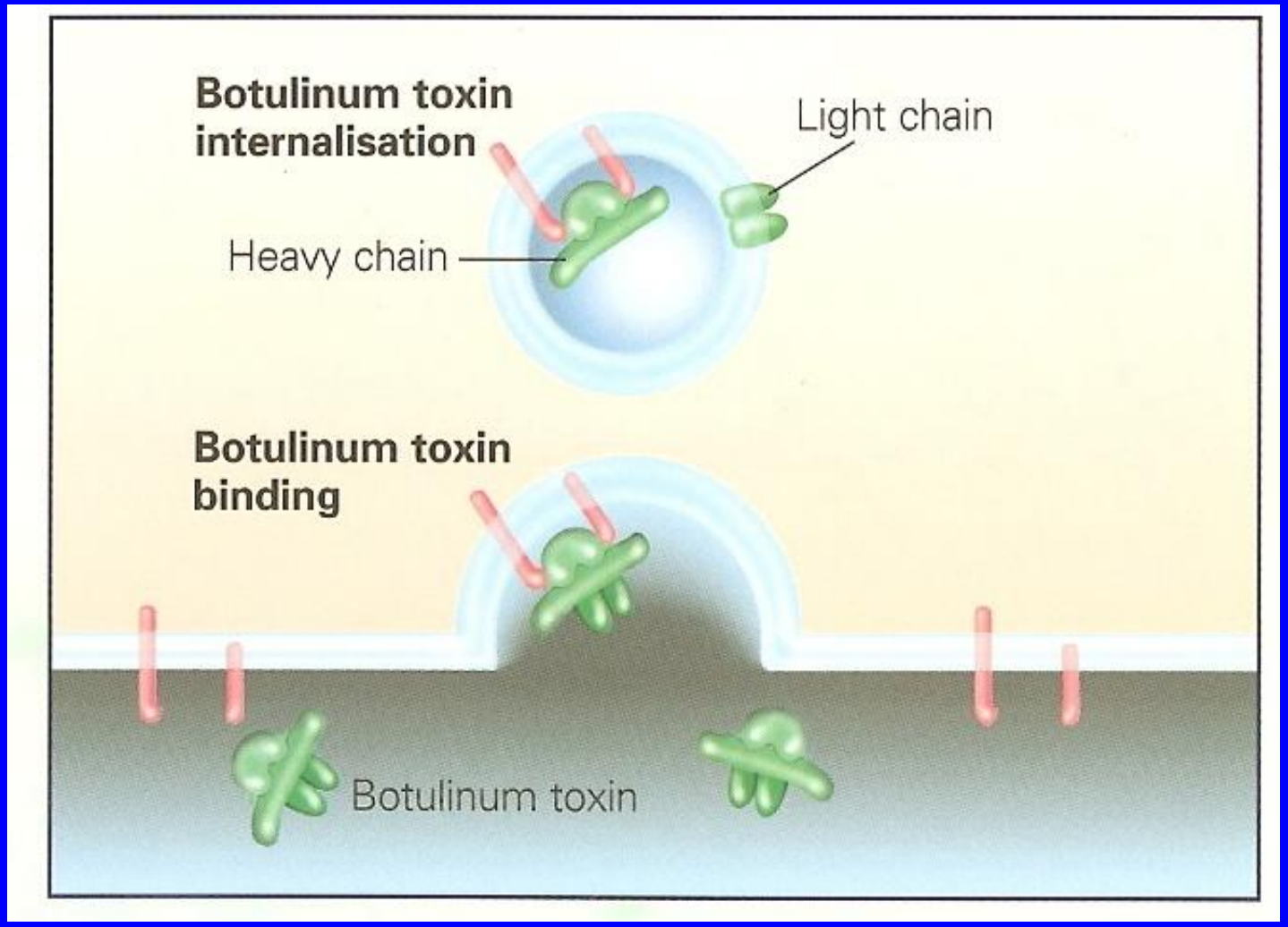
  Neurodegenerative disorders

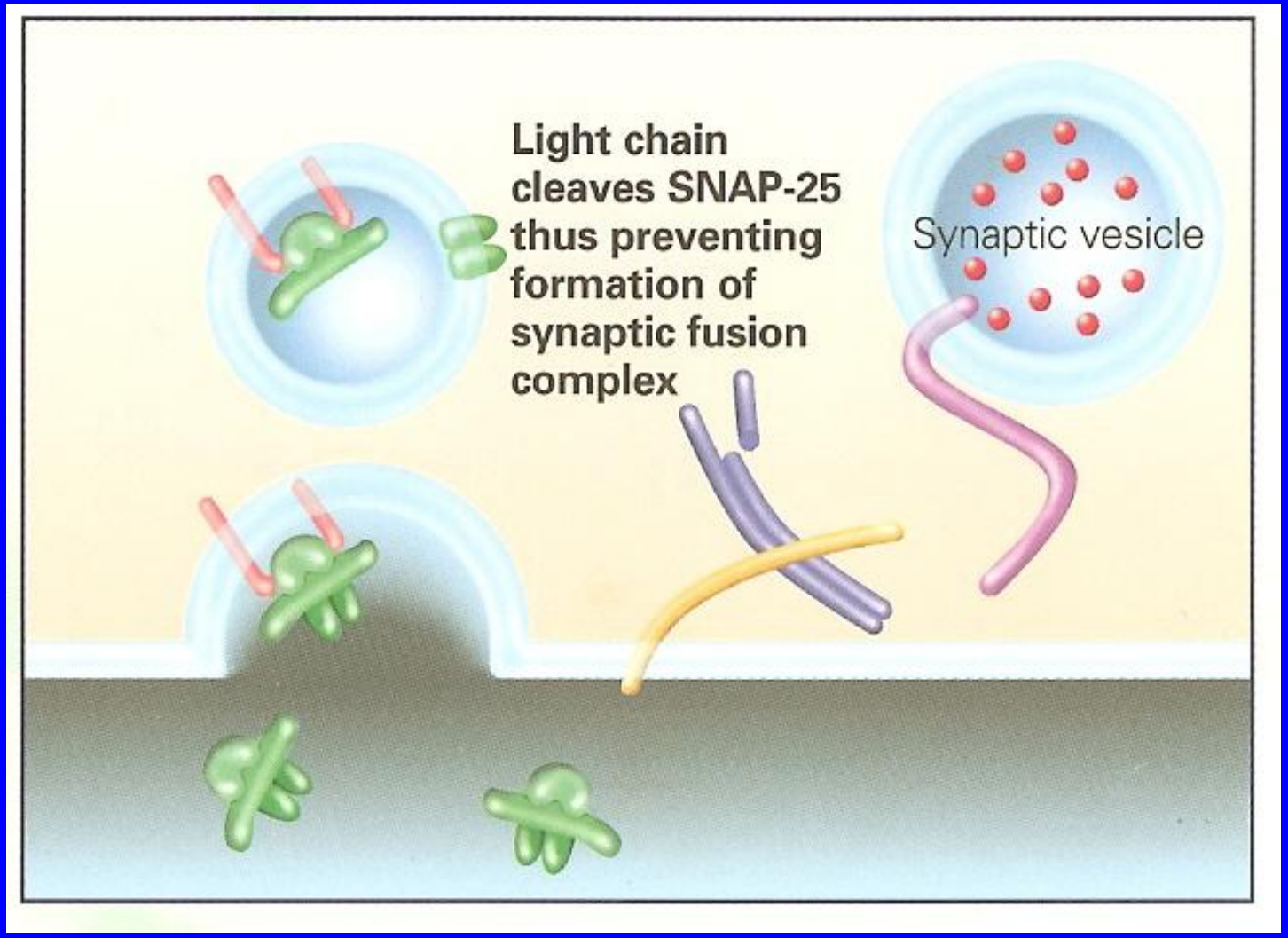
Botulinum Toxin

- Derived from the Gram – positive spore forming anaerobic bacteria *Clostridium botulinum*
- 8 toxins known; A,B,C1,C2,D,E,F and G
- Produced as a single polypeptide but cleaved to the active toxin in the form of a two chain polypeptide (heavy and light chains) bound by disulphide and non covalent bonds


Normal neuromuscular transmission
Key
Botulinum toxin
Heavy chain
Light chain
Synaptic vesicle
Acetylcholine
ACh receptor
SNARE complex
SNAP-25
Synaptobrevin
Syntaxin


Synaptic Vesicle
SNARE proteins form synaptic fusion complex
Synaptobrevin
Acetylcholine
SNAP-25
Syntaxin
Neurotransmitter released
Muscle Cell
Acetylcholine Receptors


Botulinum toxin internalisation
Light chain
Heavy chain
Botulinum toxin binding
Botulinum toxin


Light chain
cleaves SNAP-25
thus preventing
formation of
synaptic fusion
complex
Synaptic vesicle

Botulinum Toxin

- Botulinum taken up by neuromuscular junction within 12 hours
- Initial response within 3 days, maximising at 7 to 10 days
- Neuromuscular connection re-established at 12 – 16 weeks, but benefit may continue long after that
- Re-injection interval approx 12 months

Botulinum Toxin

- Local Muscle relaxant – highly selective for peripheral nerve terminals containing acetylcholine – preventing its release.

As a result;

- Reduced muscle contraction decreases dynamic tone
- Relaxed muscle allows longitudinal growth

Service Delivery

- Consultant lead
- Dedicated physiotherapist
- Assessment in the Child Development Centre
- Treatment in the Paediatric Day Unit

Referrals

- Local and Regional referrals
- Consultant Paediatricians
- Consultant Orthopaedic Surgeons
- Physiotherapists with Consultant or GP approval

Assessments

- Full consultation with family and local physiotherapist at the Child Development Centre.
- Information book given

Assessments

- Measurement of joint ranges
  especially dynamic component
- Video gait analysis
- GMFM
- Set goal for treatment
- Injection date given within 6 weeks

Patient selection

- A child should be considered for BTX-A where there is focal, dynamic spasticity and/ or dystonia
- This may be in ambulant children where the walking gait and stability of walking are poor
- It may be in non ambulant children where seating, care, personal hygiene are an issue
- It can be used for pain / spasm

Patient selection – Age

Research supports the use of BTX-A in all ages but younger children <8 are most appropriate

This may be because they are less likely to have fixed contractures, or to have learnt compensatory movement

BTX-A may be appropriate in the Older child who still has a dynamic component when used in conjunction with other treatment modalities

Patient selection - Muscle Groups

- Most commonly injected sites are gastrocnemius and soleus – extensive studies show clinical improvement and functional outcome
- Fewer studies but successful outcomes on tibialis posterior, peroneii, hamstrings, hip adductors and flexors
- Suggestion that injection of hip adductors reduces rate of hip dislocation

Injections

- Paediatric Day Unit

Injections

- Some children have sedation for the proceedure
- Oral Midazolam (0.7mg/Kg)

Botulinum Injection

- Injection sites - identified and skin ‘frozen’ with cold spray to numb area

- EMG not used

Botulinum Toxin

Type A used

Two therapeutic preparations;

Ipsen – DYSPORT approx 15 units/Kg (hemiplegia)

Allergan – BOTOX approx 6 units/KG (hemiplegia)

Injections

- Children must wait 30 minutes post injection
- Those having had sedation must wake fully and eat lunch

Botulinum Toxin

- Side Effects - Rare
- 36 clinical trials over 15 years - no serious adverse event PRNewswire June 2004
- Mild flu like illness
- Muscle weakness especially on coming out of casts
- Asked to avoid stress and ‘impact’ for a couple of weeks
- Incidence of antibodies and resistance yet to be fully evaluated

Post Injections

- Following injection there is no restriction of activity
- One week post injection, below knee walking plasters are applied
- This is changed at 7days and recast for a further week
- AFOs are refitted and final cast used as a night splint

Follow up

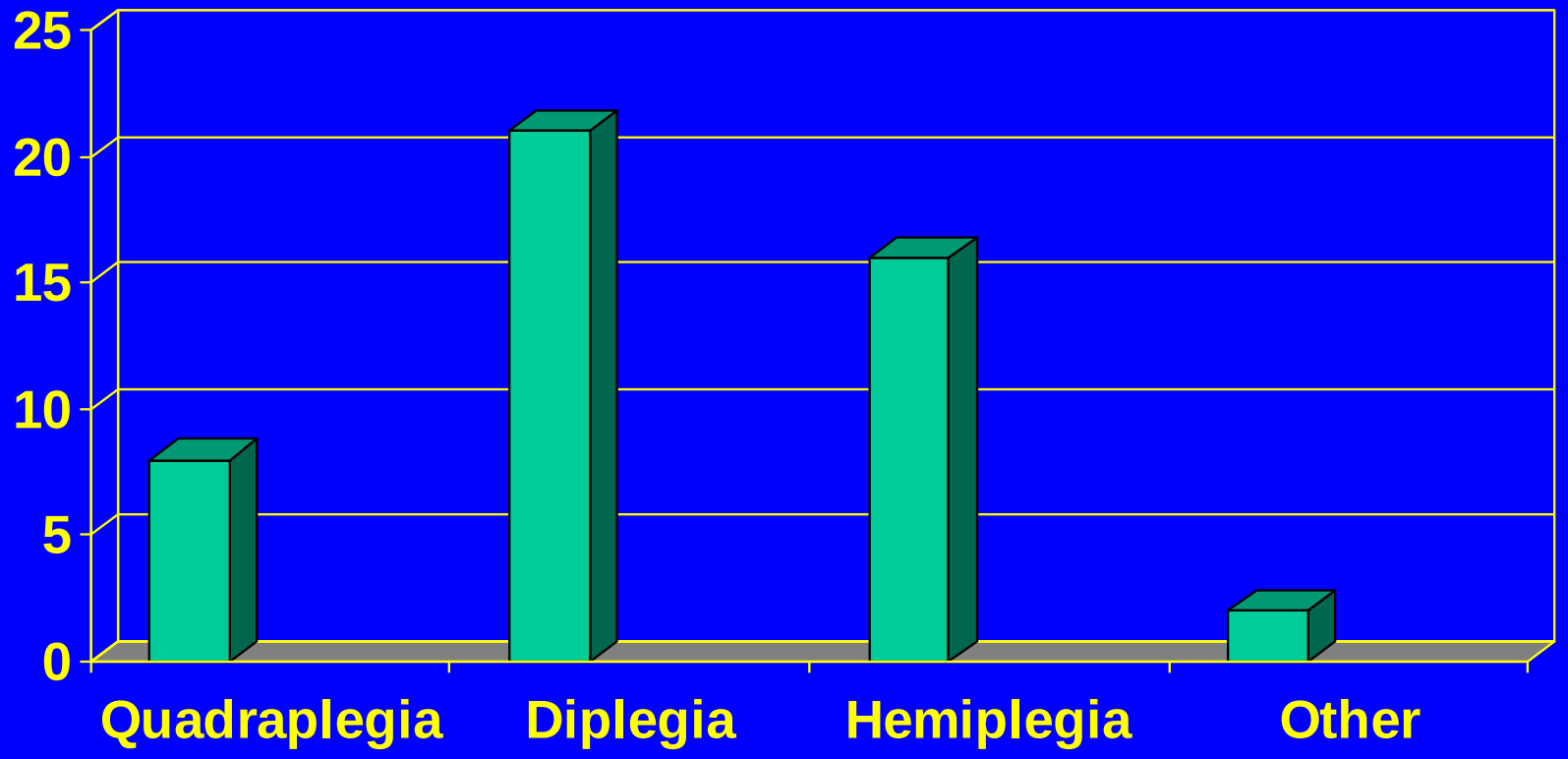
- Follow up at 6 to 8 weeks with repeat assessment
- Check for side effects
- Discharge back to local team

50 Children referred in first 4 years

- Additional 4 injected post hip surgery
- 35 children - 1 injection
- 12 children - 2 injections
- 3 children - 3 injections

- 72 in total (average 29 per year)
- This figure is now 70 to 80 referrals each year

Clinical Presentation



Results

- No child was worse at 6 week assessment
  2 children required AFOs at 4 weeks post cast removal
- One child showed no improvement
- All other children improved with measurable reduction in the dynamic catch (the average reduction was by 20 degrees)

Complications

- 2 children had marked weakness on coming out of serial casts
  - required AFO support to walk- resolved by 6 weeks
- One child jumped out of climbing frame - fractured foot
- One child went back to playing Rugby- head injury
- No Neurological complications
- No flu like illness

Patient selection - Cautions

- Fixed contractures
- Established bony deformity
- Marked muscle weakness
- Generalised spasticity
- Poor motivation or lack of post treatment physiotherapy

Botulinum Toxin

- Long Term outcome
- Normality of muscle growth
- Long term improvement in gait
- Reduction in need for orthopaedic surgery

Upper limbs

- Injection of upper limb with BTX-A shows improvement in cosmesis but little change in function although more recent studies gave been encouraging

Future

- Further work on long term effects
- Comparison with other treatments and alongside other treatments
- New treatments are evolving – Botulinum treatment may form an early treatment option or remain a localised treatment

Declaration

- Product use Ipsen Dysport
- Trainer in Assessment and Injection techniques for Ipsen