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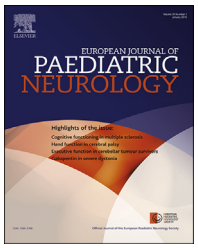

Original Article

Gabapentin can significantly improve dystonia severity and quality of life in children

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ABSTRACT

Introduction: Gabapentin has been used in the management of neuropathic pain, epilepsy and occasionally movement disorders.
Methods: A four-year retrospective, observational study analysed the use of gabapentin for severe dystonia in children at the Evelina London Children's Hospital. Motor severity was classified according to the Gross Motor Function Classification System (GMFCS), Dystonia Severity Assessment Plan (DSAP) and levels of impairment in activities of daily living were graded according to the WHO International Classification of Functioning, Disability and Health, Children & Youth version (ICF-CY) before and after gabapentin.
Results: The majority of the 69 children reported were level 5 GMFCS (non-ambulant). The DSAP grade fell significantly from grade 3 before to grade 1 after gabapentin. Significant improvements in median ICF-CY grades were seen following gabapentin in sleep quality, sleep amount, mood & agreeableness, pain, general muscle tone, involuntary muscle contractions and seating tolerance ($p < 0.01$ in all areas). A significantly higher mean dose of 18.1 mg/kg/dose (SD: 13.3) for dystonia, compared to 7.61 mg/kg/dose (SD: 4.14) for pain relief without dystonia ($z = -2.54$, $p = 0.011$) was noted.
Discussion & conclusion: Gabapentin may significantly ameliorate dystonia severity and improve activities of daily living and quality of life in children with severe dystonia.

Abbreviations: GMFCS, Gross Motor Function Classification System; DSAP, Dystonia Severity Assessment Plan; ICF-CY, WHO International Classification of Functioning; Disability and Health, Children & Youth; ELCH, Evelina London Children's Hospital; GABA, gamma-aminobutyric acid; ADL, activities of daily living; DBS, deep brain stimulation; ITB, intrathecal baclofen.

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1. Dystonia

Dystonia is a movement disorder characterised by involuntary muscle contractions that are sustained or rapidly fluctuating, resulting in abnormal postures of limbs or the whole body with repetitive twisting movements[1] affecting 33/100,000 population[2,3] and classified into 'primary' or 'secondary' causes.[4] Primary dystonias have only dystonic movements, and neuroimaging is normal.[3,4] Secondary dystonias are arise from many causes, e.g. the 'cerebral palsies' following prematurity, perinatal hypoxia, kernicterus and other vascular, structural or neurometabolic injuries to the developing brain.[5]

The natural history of dystonia varies according to cause. Primary dystonias may plateau in severity.[6] Dopa-responsive dystonias can recover completely with levodopa treatment.[7] But for most children, dystonia exerts a significant, life-long reduction of activity and participation.[8,9] A recent large, UK, supra-regional, demographic study of the management of hypertonus in children reported that less than 8% of all referred dystonia cases improved: in fact dystonia severity in primary, secondary and heredodegenerative dystonias aetiologies respectively worsened in 60.2% or remained at best static in 31.5%. giving a bleak prognosis for spontaneous improvement.[9]

2. Current management

The management of dystonias, are summarised in Table 1, mostly failing to eliminate dystonia completely or efficacious only in certain subtypes or individuals.[10] Adverse effects of anti-dystonic medication, particularly sedation, are dose-limiting in 2/3 of cases in our cohort[9] (unpublished data).

2.1. *Gabapentin*

Gabapentin, used in partial seizures,[11] is an analogue of gamma-aminobutyric acid, but neither acts as a GABA agonist or antagonist. Mechanisms of action of gabapentin are largely unknown. Gabapentinoid drugs interact with alpha subunits ($\alpha_2\delta$-1 and $\alpha_2\delta$-2) of voltage-gated calcium channels.[12] Thrombospondin, an astrocyte-secreted protein, promotes synaptogenesis in the central nervous system, acting on the $\alpha_2\delta$-1 receptor. Gabapentin antagonizes thrombospondin binding to $\alpha_2\delta$-1 receptors, thus inhibiting the synthesis of glutaminergic excitatory synapses in vitro and in vivo.[13]

Gabapentin is used in neuropathic pain syndromes such as post-herpetic and trigeminal neuralgia[14] with limited use in movement disorders.[14] *Gabapentin enacarbil*, a gabapentin precursor has some efficacy in restless leg syndrome (RLS),.[15] Pregabalin, a recently developed derivative of gabapentin with a similar profile[16] was superior in double–blind trials to dopamine agonists such as pramipexole in RLS and thought to act on separate pathways from striatal dopaminergic neurones.[17]

Use of gabapentin for familial paroxysmal dystonic choreoathetosis led to a reduction in dystonia symptoms and reduced frequency of dystonic episodes which returned on the sudden discontinuation of gabapentin as described previously.[24]

The management of childhood dystonia is challenging, particularly status dystonicus or 'brittle dystonia'.[18] Anecdotal evidence exists for gabapentin use in adult movement disorders (RLS & Wilson's Disease) but use in childhood, including severe dystonic cerebral palsy (CP) has not been reported. This study aims to:

1. Evaluate the use of gabapentin in a cohort of children with dystonia at the Evelina London Children's Hospital (ELCH)
2. Explore the dosage range of gabapentin in childhood dystonia
3. Examine the use of gabapentin as mono or adjunctive therapy for childhood dystonia

What is known about this subject

- Refractory dystonia in children is difficult to manage.
- Gabapentin antagonizes binding of thrombospondin to voltage-gated calcium channel $\alpha_2\delta$-1 receptors and inhibits synthesis of glutaminergic excitatory synapses with compelling class one evidence of benefit in restless legs syndrome.
- Little is known about gabapentin in dystonia.

What this paper adds

- Gabapentin can provide significant relief of childhood dystonia
- Gabapentin relieves dystonia-related pain, poor sleep, distress and lack of contentedness
- Gabapentin can improve activity and participation in children with severe dystonia not responding to conventional management.

3. Methods

A retrospective, observational cohort study was performed on a series of children with dystonia attending ELCH.

3.1. *Participants*

Children treated with gabapentin from January 2009 to January 2014 were identified from the ELCH pharmacy database and included in the analysis if they had a diagnosis of dystonia. Motor severity was classified using the Gross Motor Function Classification System (GMFCS)[20] for locomotor ability as follows: Level I: athletic mobility to level V: non-ambulant.[19] Children with gabapentin use without movement disorder were analysed as a pain-relief comparator group.

3.2. *Measures*

The WHO International Classification of Functioning, Disability and Health, Children & Youth version (ICF-CY) was used to grade function of activities of daily living (ADLs).[19] The newly defined Dystonia Severity Assessment Plan (DSAP) grading was also used (Table 2).[21] This is a parent/carer/allied