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RESEARCH ARTICLE

ROLE OF GABAPENTIN IN CHELATION ASSOCIATED STATUS DYSTONICUS IN WILSON'S DISEASE

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ABSTRACT

Status dystonicus is a life threatening neurological emergency which occurs secondary to etiologies like cerebral palsy, neurodegenerative disorders etc. Status dystonicus after initiation of chelation therapy with penicillamine in cases of Wilson's Disease is not unknown and is generally refractory to usual antidystonic medications. We report a case of 10 year old male with Wilson's Disease who developed status dystonicus after initiation of Penicillamine and was subsequently managed with Gabapentin as antidystonic medication for acute status dystonicus as well as long term therapy. This case illustrates the hitherto under recognised role of gabapentin as rescue medication in penicillamine induced status dystonicus in cases of Wilson's Disease not just in acute phase but as long term antidystonic medication as well. More scientific evidence is required to establish formal pediatric dosing and duration of therapy for gabapentin for this medication.

INTRODUCTION

Status dystonicus is a rare but life threatening neurological emergency and represents the most severe form of dystonia requiring hospital admission. It is characterised by generalised dystonic spasms which may be either tonic or phasic. Status dystonicus has been reported in cases of Wilson's Disease following initiation of chelation therapy with Penicillamine; which is refractory to usual antidystonic medications. There is limited evidence regarding role of gabapentin in dystonia. We report a case of penicillamine induced status dystonicus responding to gabapentin in acute phase along with reduction in baseline dystonia on prolonged treatment. A written consent was sought from the legal guardians of the index child to publish the findings, however ethical clearance was waived for this being a retrospective anonymous case report.

Case

A 10 year old male child presented with complaints of increased tone of whole body for 1 year. The parents also noted lability in mood and change in speech. Birth history was uneventful and child's development prior to onset of symptoms was comparable to peers. Examination was significant for dysarthria and dystonia which corresponded to Dystonia Severity Action Plan (DSAP) Grade 2[1]. KF ring was seen on slit-lamp examination. Investigations revealed serum ceruloplasmin of 25mg/dl which was within reference range of lab (20-60mg/dl); 24 hour urinary copper of 936 mcg/24 hrs (lab reference range: <60 mcg/24hrs) and LFT revealed increased transaminases (ALT- 136U/L & AST- 91U/L). CT brain was significant for basal ganglia calcification. Inspite of normal serum ceruloplasmin, diagnosis of Wilson's Disease was established based on the scoring system proposed by 8th International Meeting on Wilson's disease, Leipzig 2001[2]. Mutational analysis to confirm diagnosis was not possible due to economic constraints. Child was started on penicillamine (20mg/kg/d), zinc (75mg/d) and baclofen (0.4mg/kg/d). However a week after starting penicillamine, dystonia markedly increased and child was unable to take feeds orally. The severity of dystonia on increased to DSAP Grade 4. Considering penicillamine induced status dystonicus, it was withdrawn and diazepam (0.2 mg/kg/d) was added to counter dystonia. On non improvement, dose of diazepam and baclofen was titrated up (0.5mg/kg/d) and (0.7mg/kg/d) respectively while trihexyphenidyl was added (0.6mg/kg/d) further titrated (1.3mg/kg/d). Further increase in status dystonicus prompted addition of gabapentin (40mg/kg/d) as rescue medication. After 2weeks some resolution in dystonia was noted and severity reduced to DSAP 3. Subsequently, diazepam was withdrawn, dose of trihexyphenidyl reduced but Gabapentin was continued on discharge. 3 months post discharge, Penicillamine was again introduced at a lower dose of 8mg/kg/d, under cover of these medication but an apparent deterioration in dystonia led to discontinuation. Our plan of introducing Trientine in lieu of Pencillamine could not be executed due to unavailability of Trientine. Currently, child is in our follow up with a therapeutic plan of copper free diet,

Zinc, Baclofen and Gabapentin dystonia has reduced to DSAP Grade 1 and continues to improve.

Table 1 Dystonia Severity Action Plan (DSAP) Scale[1]

Grade	Severity
1	Sits comfortably; regular periods of uninterrupted sleep
2	Irritable; dystonic postures interferes with sitting; can only tolerate lying
3	Not able to tolerate lying; sleep disturbed; no metabolic decompensation with creatinine kinase < 1000 IU/L
4	Not able to tolerate lying; sleep disturbed; pyrexia in absence of infection; evidence of metabolic decompensation; creatinine kinase > 1000 IU/L; myoglobinuria
5	Features of Grade 4 with full metabolic decompensation; respiratory/cardiovascular/renal compromise

DISCUSSION

Dystonia is defined as a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both[3]. It leads to overflow muscle activation, often initiated or worsened by voluntary action. Status dystonicus is the most severe form of generalised dystonia requiring hospital admission[4]. Grading the severity of dystonia eludes consensus however newly proposed Dystonia Severity Action Plan (DSAP) is simple scale to assess trajectory of dystonia (Table 1)[1]. Dystonia in children can be caused by diverse etiologies ranging from rare primary form (genetically determined) to relatively common secondary dystonia caused by cerebral palsy, encephalitis, vascular diseases, neurodegenerative disorders, drugs amongst others.

Neurologic deterioration in form worsening dystonia to the extent of status dystonicus after initiation of chelation through penicillamine in Wilson's Disease is well documented[5]. The pathogenesis of this worsening of dystonia is unclear but basal ganglia, thalamus and brainstem injury mediated by increased copper turnover following intiation of chelation is hypothesised based on MRI evidence of signal changes in these locations[6]. Penicillamine induced status dystonicus is often refractory to usual antidystonic medications like baclofen, diazepam, trihexyphenidyl, haloperidol. There is evolving evidence regarding use of Gabapentin in successful management of dystonia[7] and there are reports of favourable response in acute status dystonicus in cases of Wilson's Disease[8]. Gabapentin antagonises thrombospondin binding to α2-δ1 receptors, thus inhibiting the synthesis of glutaminergic excitatory synapses in vitro and in vivo[9] and this may be the putative mechanism of action of gabapentin in dystonia.

In our case, Gabapentin was beneficial not only in acute phase of penicillamine induced status dystonicus but was effective against reducing the baseline dystonia. In view of paucity of available literature regarding use of gabapentin in childhood dystonia, decision of 900mg/d (40mg/kg/d) was empirical and guided by an earlier report[8] and prolonged usage at this dose was not associated with any side effects. In our 18 month follow up, child's dystonia reduced from DSAP4 to DSAP1.

Gabapentin is devoid of sedative effects of conventional antidystonic medications. In our index case, addition of gabapentin helped us withdraw diazepam along with reducing dose of baclofen and trihexyphenidyl, which had a definite positive effect in child's interactions and daily activities.

CONCLUSION

Gabapentin may be considered as a rescue medication for penicillamine induced status dystonicus in Wilson's Disease. In our case, it was useful as a long term antidystonic medication as well. More robust scientific evidence is needed to formalise gabapentin's pediatric doses and duration of therapy for this indication.

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