Levodopa-Responsive Chorea: A Review

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Abstract

Background: Chorea is one of the disabling movement disorders, and the number of drugs which can treat this disorder effectively is limited. Tetrabenazine and deutetrabenazine are the two drugs approved by the US-FDA for the treatment of chorea associated with HD. Levodopa can improve chorea in some disorders, and this review aims to provide information on the use of levodopa in chorea. **Methods:** A literature search was performed in February 2019 using the following terms "levodopa chorea," "levodopa TITF-1," levodopa brain-lung-thyroid syndrome," and "levodopa Huntington's Disease." The information regarding the etiology, outcome, and dose of levodopa was collected. **Results:** We found a total of 18 cases in the literature where the benefit was reported with levodopa. Majority of the cases were brain-thyroid-lung (BTL) syndrome (50%). Another 5 cases were HD (Huntington's Disease), one with PCH type 2 (Pontocerebellar hypoplasia type 2), one with meningovascular syphilis, and two patients with Sydenham chorea. The patients with BTL syndrome responded to a very low dose of levodopa. **Discussion:** This review suggests that levodopa has the potential to improve chorea in BTL syndrome while its use in chorea due to other disorders requires further study. BTL syndrome due to NKX2-1 mutation responded to levodopa while we did not find any case of chorea due to ADCY-5 mutation responding to levodopa.

Keywords: Chorea, hereditary chorea, huntington disease, levodopa

Introduction

Chorea is one of the hyperkinetic movement disorders which is characterized by unpredictable, non-patterned, and involuntary movements which give an appearance of fidgetiness.[1,2] There are several causes of chorea which include: Autoimmune, vascular, paraneoplastic, genetic, metabolic, etc.[1,2] Chorea results from the dysfunction of either direct or indirect pathway operating within the basal ganglia.[1,2] A lesion within the indirect pathway such as subthalamic nucleus (STN) or stimulation of the direct pathway which is seen with levodopa use can lead to choreiform movements.[1,2]

The treatment of chorea should be directed at the underlying cause (if treatable).[1,2] Symptomatic treatment of chorea should be considered if the movements are disabling.[1,2] Currently, tetrabenazine and deutetrabenazine are the only two agents approved by the US FDA for the treatment of chorea associated with Huntington's disease (HD).[1,2] These two agents are dopamine depletors and decrease chorea by reducing the stimulation of the direct pathway and increasing the activity of the indirect pathway.[1,2] Their use is associated with depression, sedation, parkinsonism, etc.[1,2] Other strategies to treat chorea include blocking post-synaptic dopamine receptors with typical or atypical neuroleptics.[1,2] Amantadine, riluzole, anticonvulsants, and benzodiazepines are some of the other drugs which can help chorea in some patients.[1,2]

Levodopa can also reduce chorea paradoxically by lowering the sensitivity of post-synaptic dopamine receptors due to continuous stimulation.[3] Similarly, dopamine agonist can reduce dopamine release by stimulating pre-synaptic receptors.[3] The information on the use of levodopa in the treatment of chorea is limited. This paper aims to review the literature on the symptomatic treatment of chorea with levodopa, limitations of using levodopa in chorea, and whether the response is related to the underlying etiology of chorea.

Methods

A search of PubMed database was performed using the terms "levodopa chorea," "levodopa benign hereditary chorea," "levodopa TITF-1," "levodopa brain-lung-thyroid syndrome," and "levodopa Huntington's disease." This search was performed in February 2019, and all the articles published in the English language were included. We also included a case report which was presented as an abstract at the American Academy of Neurology meeting.[4] Our strategy revealed more than 300 articles. We further included relevant articles after reviewing the reference list of identified articles. Only 11 case reports/case series were selected for a final review. We found a case report of dopamine-agonist responsive chorea which

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was not included because this article will focus exclusively on levodopa responsive chorea.[5]

Results

Eighteen cases of levodopa responsive chorea were identified [Table 1]. Nine of the 18 patients had the diagnosis of brain-thyroid-lung syndrome (BTL), also known as benign hereditary chorea. All patients with BTL were children ranging from 2 to 9 years of age. The dose of levodopa varied widely and was often weight based without a reported weight. Dosage of levodopa ranged from 2 mg/kg/day to 6 mg/kg/day in cases of BTL. Five of the 18 patients had the diagnosis of HD. They ranged from 42 to 52 year of age, and 4 out of 5 were female. Other medications tried and failed included fluphenazine, perphenazine, haloperidol, thiopropazate, and chlordiazepoxide. One reported case of HD did not provide details of the patient's age, sex, levodopa dose, or other medications tried. Two of the total 18 patients had the diagnosis of Sydenham chorea (SC). Both patients were male teenagers, 18 and 13 years of age. Both were treated with levodopa in combination with MK486 (peripheral Dopa decarboxylase inhibitor). Last, there were single case reports with pontocerebellar hypoplasia type 2 (PCH 2) and meningovascular syphilis-related chorea which were levodopa responsive. The patient with PCH 2 was a 9-year-old female whose chorea responded to carbidopa/levodopa at a dose of 50/200 mg a day. The patient with meningovascular syphilis-related chorea was a 70-year-old male treated with an unreported dose of levodopa in combination with penicillin.

Discussion

Cases of levodopa responsive chorea are sparse and involve multiple different etiologies making a unifying mechanism for benefit very unlikely. Most cases are seen with benign hereditary chorea (BHC), also known as bran thyroid lung syndrome (BTL) when the phenotype expands from chorea alone. In recent years it has been discovered to be due to mutations in NKX2-1 gene (formerly TITF-1) on chromosome

Table 1: Published Reports of Levodopa Responsive Chorea

Source	Age (in years)	Sex	Diagnosis	Response	Other medications tried
Asmus *et al*., 2005[6]	2	F	BTL	Levodopa 20 mg/kg/day for 6 weeks then 7 mg/kg/day three times a day + 1 mg trihexyphenidyl	n/a
	2.5	M	BTL	Levodopa 20 mg/kg/day	n/a
Ferrara *et al*., 2011[7]	2.5	F	BTL	Carbidopa/levodopa 25/100 mg six tablets daily	n/a
	9	M	BTL	Carbidopa/levodopa 25/100 mg three times a day	n/a
	3.5	M	BTL	Carbidopa/levodopa 25/100 mg three times a day	n/a
	4	M	BTL	Carbidopa/levodopa 25/100 four times a day	n/a
Fons *et al*., 2012[8]	3.5	F	BTL	Levodopa 9 mg/kg divided twice a day for 6 months then maintained on 3 mg/kg/day for 11 months	n/a
Rosati *et al*., 2014[9]	3	F	BTL	Levodopa 7 mg/kg/day	n/a
Shukla *et al*., 2017[4]	2	M	BTL	Carbidopa/levodopa 25/100 mg three times a day	n/a
Tan *et al*., 1972[10]	46	F	HD	Levodopa 5 g/day	Haloperidol, thiopropazate, chlordiazepoxide, chloral hydrate, paraldehyde, chlorpromazine, pericyazine
Schenk and Leijnse-Ybema, 1974[11]	n/a	n/a	HD	Unknown dose	Thiopropazate
Michaelides, 1975[12]	52	M	HD	Levodopa 6 g/day	Trihexyphenidyl, chloral hydrate, diazepam, chlorpromazine
Loeb *et al*., 1976[13]	52	F	HD	Levodopa 2 g/day	Fluphenazine 100 mg a day
	42	F	HD	Levodopa 2 g/day	Perphenazine 40 mg a day
Spissu *et al*., 1975[14]	18	M	SC	Levodopa 10 mg/kg + MK486 (peripheral Dopa decarboxylase inhibitor)	n/a
	13	M	SC	Levodopa 1 mg/kg + MK486 (peripheral Dopa decarboxylase inhibitor)	n/a
Grosso *et al*., 2002[15]	9	F	PCH 2	Carbidopa/levodopa 50/200 a day	n/a
Blakeley and Jankovic, 2002[16]	70	M	Meningovascular syphilis	Unknown dose + penicillin	n/a

BTL: Brain Thyroid Lung Syndrome; HD: Huntington's Disease; SC: Sydenham Chorea; PCH 2: Pontocerebellar Hypoplasia Type 2

14.[17] NKX2-1 is thought to play a role in the development of the striatum and an autopsy study has shown a reduction of striatal interneurons.[18] Animal models have shown that disruption of NKX2-1 disturbs normal migration of dopaminergic neurons.[19,20] Also, a dopaminergic brain imaging study found a decrease in dopamine receptor binding in patients with NKX2-1 mutations.[21] The role of levodopa in the treatment of chorea in these cases is likely directly attributable to the developmental defects which disrupt dopaminergic pathways. We found a case report of BTL syndrome where the patient did not respond to levodopa but had a good response to ropinirole which implies the involvement of dopaminergic pathways in this disorder.[5] Long-term follow-up of this disorder has shown that chorea improves or stabilizes in the majority of the patients and the term "benign" is used for this reason.[22] However, some patients have mental retardation and disabling myoclonus.[22] Interestingly; we did not find any case of levodopa responsive chorea due to ADCY5 mutation.[23]

All cases of levodopa responsive chorea in HD are from the early to mid-1970s. The approach at the time focused on homovanillic acid (HVA), a dopamine metabolite. Schenk and Leijinse-Ybema argued the existence of two types of HD, one with normal CSF HVA levels and one with low HVA levels.[11] They further argued that HD with low HVA would respond well to levodopa.[11] This claim was directly refuted in a larger study by Sishta and Templer in which they treated 16 HD patients with levodopa, and they found most patients to worsen whereas none had improvement.[24] Further, there was no correlation between low HVA level and levodopa responsiveness.[24] No further cases of levodopa responsive chorea in HD have been reported since the publication of this study. Another possibility of levodopa responsive chorea in HD could be sedation, and the use of concomitant anti-dopaminergic agents might have helped chorea as well.[10,12] It is interesting to note that a levodopa provocative effect on chorea was studied in patients at a higher risk of HD.[25] This study did not show any false positives in the control group.[25] A double-blind, randomized, and cross-over trial was performed with apomorphine subcutaneous infusion in patients with HD.[3] Of the nine patients recruited, only five patients responded to the treatment as documented by the improvement in Unified Huntington's Disease Rating Scale (UHDRS).[3] It is possible that this benefit is due to the activation of presynaptic dopamine receptors leading to a reduced dopamine turnover or sedation due to apomorphine.[26] However, studies involving the use of dopamine agonist with a large sample size are lacking, and it is difficult to draw a definite conclusion at this time.[26]

Another form of chorea (dyskinesia) which responds to levodopa is diphasic dyskinesia seen in Parkinson's disease (PD). This is also called as "low-dose" dyskinesia which responds to an increase in the dose of levodopa.[27] This type of chorea (dyskinesia) is predominantly seen in the lower extremities.[27]

The two cases of Sydenham Chorea (SC) that were reported to respond to levodopa were reported in 1975.[14] CSF HVA was also checked in the patients before and after treatment and showed a significant increase indicating increased dopamine turnover which is to be expected.[14] SC is due to antibodies directed at group A β-hemolytic streptococcus which in turn cross-reacts with cells in the basal ganglia.[28] A precise mechanism for levodopa responsiveness is not known. In this case report, MK486 was used along with levodopa. MK486 is a peripheral decarboxylase inhibitor L-alpha-methyl-dopahydrazine.[29] MK486, when given in combination with levodopa, showed a reduced incidence of nausea and vomiting and more improvement compared to levodopa alone.[29]

A case of dystonia and choreoathetosis due to pontocerebellar hypoplasia (PCH) type 2 was levodopa responsive. PCH is an inherited neurodevelopmental disease characterized by the decreased growth of infratentorial structures especially the pons and cerebellum and later degeneration of supratentorial structures including the basal ganglia and cerebral cortex.[30] Patients with PCH type 2 classically develop dyskinetic crisis consisting of dystonia and choreoathetoid movements. These movements are likely due to the involvement of infratentorial structures, notably the substantia nigra, which may explain the reason for levodopa responsiveness.[15]

Limited details are available about the case of chorea due to meningovascular syphilis. The patient was also treated with intravenous penicillin which may have played a more significant role in the resolution of chorea than concurrent levodopa administration.[16]

Conclusion

The developmental abnormalities in the dopaminergic system of BTL syndrome patients due to the NKX2-1 gene explains the benefit of levodopa. BTL syndrome is a rare entity, and a multi-center randomized clinical trial may help to justify the use of levodopa as a first line agent. Levodopa does not have long-term side effects (such as parkinsonism and akathisia) when compared to dopamine-depleting agents which can potentially make levodopa a preferred agent to treat chorea.[1] We did not find enough level of evidence to propose the use of levodopa in treating chorea seen with other disorders. A lack of convincing physiologic mechanism and the potential for worsening of symptoms should caution practitioners in its usage with other disorders leading to chorea.

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Conflicts of interest

There are no conflicts of interest.

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