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Long-term safety and effectiveness of pramipexole in tetrahydrobiopterin deficiency

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ABSTRACT

Tetrahydrobiopterin (BH_4) deficiencies are inherited neuro-metabolic disorders leading to monoamine neurotransmitters deficiency. An individualized replacement therapy with neurotransmitters precursors is necessary to restore dopaminergic and serotoninergic homeostasis. The correction of dopaminergic tone is complicated, like in Parkinson disease, by L-dopa short half-life and adverse effects. To improve this picture, since 2009 we introduced the non-ergot dopamine agonist pramipexole as an adjunct to L-dopa therapy in the treatment of the most common causes of BH_4 deficiency, 6-pyruvoyl tetrahydropterin synthase (PTPS) deficiency and dihydropteridine reductase (DHPR) deficiency. In the short-term period, this approach allowed substantial clinical advantages in affected patients, with amelioration and stabilization of the clinical picture on twice daily treatment administration and no adverse effect.

Here we describe the long-term clinical follow-up (83 ± 24 months) of seven patients with BH_4 deficiency treated with pramipexole. After a period of good clinical compensation (34 ± 1 months), different impulse control disorders (gambling, compulsive buying, and hypersexuality) were observed in three patients treated with high-dose pramipexole (0.030–0.033 mg/kg/day) beyond adolescence. These psychiatric adverse effects promptly disappeared after curtailing pramipexole dose by 50–60%. Low-dose pramipexole therapy has been safe and effective in the long-term period in all treated patients (59 ± 9 months).

High-dose pramipexole therapy in BH_4 deficiency can be complicated, like in Parkinson disease, by psychiatric adverse effects. Low-dose pramipexole therapy (~0.010 mg/kg/day) has been safe and clinically effective on long-term follow-up, representing a helpful therapeutic option in patients with BH_4 deficiency.

1. Introduction

Tetrahydrobiopterin (BH_4) deficiencies are a heterogeneous group of rare inherited neuro-metabolic disorders characterized by monoamine neurotransmitters deficiency. Taken together, 6-pyruvoyl tetrahydropterin synthase deficiency (PTPS; MIM 261640) and dihydropteridine reductase deficiency (DHPR; MIM 261630) represent about 90% of all forms of BH_4 deficiency. Both conditions result in

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hyperphenylalaninemia and impaired catecholamine and serotonin neurotransmitter production. Clinical presentation occurs soon after birth or after some months, with neurological deterioration, developmental delay, seizures, truncal hypotonia and limb hypertonia, associated with parkinsonian features. Early diagnosis is facilitated by neonatal screening for hyperphenylalaninemia and prompt treatment essential for patients' outcome.[1–3] Standard therapy is very complex. The administration of synthetic BH_4 allows the correction of peripheral hyperphenylalaninemia, but scarce effects can be obtained at the central level. An individualized neurotransmitters replacement therapy is necessary to restore dopaminergic and serotoninergic homeostasis. The correction of dopaminergic neurotransmission represents the most critical aspect in BH_4 deficiency, mainly due to L-3,4 dihydroxyphenylalanine (L-dopa) short half-life and adverse effects. Three to six daily L-dopa administrations are generally necessary for a satisfactory clinical compensation, even if inhibitors of L-dopa catabolism, such as carbidopa, deprenyl and entacapone are concomitantly administered.[1] To improve this picture, in 2009 we introduced the non-ergot dopamine agonist pramipexole as an adjunct to L-dopa therapy in a series of patients with PTPS deficiency, and in 2012 in DHPR deficiency.[4,5] Here we provide the long-term safety and effectiveness of this implemented therapeutic regimen in BH_4 deficiency.

2. Patients and methods

Seven patients with BH_4 deficiency receiving pramipexole as an adjunct to L-dopa therapy were clinically followed for 83 ± 24 months. Their characteristics and actual dopaminergic regimens are reported in Table 1. Folinic acid supplementation was administered in patients with DHPR deficiency. Satisfactory control of peripheral hyperphenylalaninemia was obtained in all patients (mean blood phenylalanine 3.7 ± 1.8 mg/dl). Clinical visits were scheduled every 3–6 months on the basis of patients' age and therapeutic response. In all patients, full clinical evaluation was regularly accomplished also by applying an adapted Unified Parkinson's Disease Rating Scale (UPDRS). The occurrence of any side effect related to pramipexole therapy was systematically investigated.

3. Results

In all patients, all the previously described advantages of the implemented L-dopa + pramipexole therapy, including the amelioration and stabilization of the clinical picture on twice daily treatment administration, were maintained during the longitudinal clinical monitoring.[4,5] On long-term follow-up, no patients experienced any common side effect of pramipexole therapy, including dizziness, fainting, drowsiness, visual hallucinations, nausea, weakness, and constipation. After a variable period of good clinical compensation, however, older patients treated with high pramipexole dosage (0.030–0.033 mg/kg/day) experienced different psychiatric side effects (impulse control disorders) referable to pramipexole therapy. These adverse effects were invariably associated with

Table 1 – Characteristics and treatment of 7 patients affected by tetrahydropterin (BH_4) deficiency due to 6-pyruvoyl tetrahydropterin synthase (PTPS) or dihydropteridine reductase (DPPR) deficiency.

Patient	Age (years)	Mutant alleles	Follow-up on pramipexole therapy (months)	Dopaminergic treatment daily administrations	Current dopaminergic treatment					Other medications	
					Pramipexole (mg/kg/day)	L-dopa (mg/kg/day)	Carbidopa (mg/kg/day)	Selegiline (mg/kg/day)	Entacapone (mg/kg/day)	BH_4 (mg/kg/day)	OH-tryptophan (mg/kg/day)
		PTPS									
1	31	T76M/D136V	34	3	–	8.4	2.1	0.14	11.4	2.4	3.7
2	27	ΔV57/Δ(K29-32)	98	2	0.013	3.2	0.8	0.14	8.6	3.0	2.5
3	16	P87L/P87L	98	2	0.006	6.4	1.6	0.13	7.7	2.9	4.8
4	13	N52S/N52S	100	2	0.008	6.4	1.6	0.08	9.7	3.9	2.0
5	7	N52S/N52S	100	2	0.009	7.1	1.8	0.17	7.1	5.2	3.9
		DHPR									
6	24	G23D/Y150C	74	2	0.014	2.4	0.5	0.09	7.5	6.0	2.0
7	9	L14P/L14P	75	2	0.017	2.7	0.7	0.09	7.1	–	4.2

steadily normal prolactin. Prompt reduction of pramipexole dose to 0.008–0.017 mg/kg/day in all but one patients allowed the disappearance of the impulse control disorders, subsequently warranting a steady optimization of patients' clinical picture. Patients' clinical reports are described below.

3.1. *Patient 1 (PTPS deficiency)*

This male patient attended normal school classes and worked as a barman. Pramipexole (0.033 mg/kg/day) was beneficial and well tolerated for 34 months, allowing substantial amelioration of motor and intellectual performances (UPDRS 12/147) as well as improvement of patient's social and working life. After this period, the patient experienced compulsive gambling. The immediate suspension of pramipexole therapy and re-introduction of standard L-dopa therapy was accompanied by disappearance of the addiction but reappearance of motor disturbances (UPDRS 25/147) and highly fluctuant hyperprolactinemia. Pramipexole was not re-introduced in this patient.

3.2. *Patient 2 (PTPS deficiency)*

This young man was able to attend normal school classes, to drive a car, to make sports (horse-riding), and to work as a civil servant. Pramipexole (0.033 mg/kg/day) warranted good clinical compensation with no reported side effects for 35 months (UPDRS 17/147). After this period, the patient experienced episodes of compulsive shopping. The temporary suspension of the L-dopa + pramipexole regimen allowed the immediate disappearance of the impulse control disorder, but worsening clinical and biochemical compensation (UPDRS 30/147). Pramipexole was then progressively re-introduced at lower dose (0.013 mg/kg/day). The patient showed optimal clinical compensation (UPDRS 17/147) with no behavioural disturbances neither other side effects until present (61 months follow-up).

3.3. *Patient 3 (PTPS deficiency)*

This male patient is severely mentally retarded. He can walk, run, and attend activities of daily living, but his cognitive ability is very poor. Pramipexole therapy (0.032 mg/kg/day) was beneficial and well tolerated for 33 months (UPDRS 40/143). After this period, parents reported episodes of hypersexuality, aggressivity, and trouble sleeping. These episodes disappeared after the reduction of pramipexole dose to 0.006 mg/kg/day, with optimized clinical compensation (UPDRS 40/143) during the next 65 months follow-up.

3.4. *Patient 4 and 5 (PTPS deficiency)*

These siblings are attending normal school classes with partial educational support. In both patients, clinical benefits of pramipexole (0.030 mg/kg/day) were not complicated by any adverse effect. Based on the clinical experience of behavioural disturbances in older PTPS patients receiving pramipexole at the same dose, pramipexole dose was reduced in both patients (0.008 and 0.009 mg/kg/day) with optimal clinical outcome after 100 months follow-up (UPDRS 6/147 and 6/143, respectively).

3.5. *Patient 6 (DHPR deficiency)*

This male patient attended regular school classes and is an office worker. Clinical advantages of pramipexole monotherapy lasted for 30 months with no adverse effects (UPDRS 8/147). Episodes of painful foot dystonia then complicated the picture. After the reintroduction of a combined L-dopa + pramipexole regimen, no further adverse effects were observed for in the next 44 months (UPDRS 8/147).

3.6. *Patient 7 (DHPR deficiency)*

This patient is attending normal school classes. After 75 months follow-up, treatment with pramipexole (0.031 mg/kg/day) was not complicated by any adverse effect (UPDRS 4/147). To prevent any clinical symptoms of dopaminergic overstimulation, pramipexole dose was set at 0.017 mg/kg/day with stable clinical compensation and no adverse effects.

4. Discussion

The correction of dopaminergic homeostasis in BH_4 deficiency is complicated, like in Parkinson disease, by L-dopa pharmacokinetics and adverse effects. During last years, we introduced different treatment implementations to ameliorate the clinical outcome of patients with BH_4 deficiency, including the use of monoamine oxidase inhibitors and catechol-O-methyltransferase inhibitors.[6,7] These drugs allowed significant clinical improvement in BH_4 deficiency, with reduction of L-dopa daily dose by 15–20%. In particular, entacapone mainly exerts its advantageous effect by reducing 3-O-methyldopa concentration and increasing L-dopa bioavailability without any increase of peak plasma L-dopa concentration.[7]

Despite these L-dopa sparing strategies, however, diurnal fluctuations of the clinical picture and a number of residual motor and behavioural disabilities are commonly reported.[8,9] Since dopamine agonists provide a more continuous dopaminergic stimulation with respect to L-dopa, we firstly proposed and successfully introduced their use in patients with BH_4 deficiency.[4,5] Pramipexole was chosen because of its documented effectiveness and safety in Parkinson disease,[10] previous use in pediatrics,[11] long half-life (8–12 h),[12] low risk of heart valve and retroperitoneal fibrosis as a non-ergot agent. We already described the short-term clinical advantages of its use as an adjunct to L-dopa therapy in BH_4 deficiency.[4,5]

In this article, we reported the long-term follow-up of patients with BH_4 deficiency receiving pramipexole. After several months of good clinical compensation, clinical course in young men with BH_4 deficiency on high-dose pramipexole therapy was complicated by different impulse control disorders, including pathological gambling, compulsive buying, and hypersexuality. These adverse effects were likely linked to dopaminergic overstimulation, as promptly resolved by curtailing by 50–60% the dose of the dopamine agonist. Actually, such a lowered pramipexole dose was well tolerated and effective even on long-term follow-up.

Impulse controls disorders became a well known complication of the use of dopamine agonists in Parkinson disease.[13–16] Although these psychiatric side effects can be

associated to the use of different dopamine-agonists, pramipexole is the medication predominantly implicated. In Parkinson disease, the onset of impulse control disorders often occurs within the first few months of pramipexole therapy, although longer latencies (24–30 months) were reported as well.[13] Symptoms generally resolve shortly after stopping the drug. Pramipexole-associated impulse control disorders, moreover, were also reported in restless legs syndrome.[17]

The molecular mechanism at the basis of these behavioural adverse effects lies in dopaminergic sensitization. D2 and D3 receptors are the primary molecular targets of the main dopamine agonists, including pramipexole. The wide-spread distribution of D3 receptors within the limbic system suggests their primary implication on clinically relevant behavioural disturbances. Prolonged stimulation by pramipexole of the high-affinity D3 receptors is associated to an increase in the number of D3 receptors and an increase of repetitive behaviours in animal models, and impulse control disorders in humans.[18] These mechanisms are likely at the basis of the occurrence of impulse control disorders even in inherited monoamine neurotransmitter disorders treated with dopamine agonists.

This is the first report of psychiatric adverse effects related to the use of dopamine agonists in BH_4 deficiency. The occurrence of compulsive behavioural disturbances was invariably evidenced after a prolonged period of optimal clinical compensation. Moreover, the pramipexole-related impulse control disorders were dose-dependent, as lowering pramipexole dose was effective in their stable resolution and prevention. Noteworthy, good clinical compensation on twice daily treatment administration was possible even after the curtailment of pramipexole therapy. The optimization of pramipexole dose in BH_4 deficiency, indeed, can be facilitated by the evaluation of a prolactin profile besides clinical assessments, potentially functional to identify dopaminergic overstimulation with risk of behavioural side effects.[19,20]

In conclusion, clinical benefits of the use of high-dose pramipexole in BH_4 deficiency beyond the adolescence can be complicated, like in Parkinson disease, by the occurrence of psychiatric behavioural adverse effects. Low-dose pramipexole therapy (~0.010 mg/kg/day) has been safe and effective on long-term follow-up, representing a helpful therapeutic option in patients with BH_4 deficiency.

Conflict of interest statement

All authors have no conflict of interest to declare.

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