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ORIGINAL ARTICLE

The effect of piracetam on ataxia: clinical observations in a group of autosomal dominant cerebellar ataxia patients

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ABSTRACT

Objectives: **Autosomal dominant cerebellar ataxias are clinically and genetically heterogeneous neurodegenerative disorders. There is no known treatment to prevent neuronal cell death in these disorders. Current treatment is purely symptomatic; ataxia is one of the most disabling symptoms and represents the main therapeutic challenge. A previous case report suggesting benefit from administration of high dose piracetam inspired the present study of the efficacy of this agent in patients with cerebellar ataxia. Piracetam is a low molecular weight derivative of γ-aminobutyric acid. Although little is known of its mode of action, its efficacy has been documented in a wide range of clinical indications, such as cognitive disorders, dementia, vertigo and dyslexia, as well as cortical myoclonus. The present report investigated the role of high dose piracetam in patients with cerebellar ataxia.**

Methods: **Eight patients with autosomal dominant cerebellar ataxia were given intravenous piracetam 60 g/day by a structured protocol for 14 days. The baseline and end-of-the study evaluations were based on the International Cooperative Ataxia Rating Scale.**

Results: **Statistical analysis demonstrated a significant improvement in the patients' total score (P = 0·018) and a subscale analysis showed statistical significance for only the posture and gait disturbances item (P = 0·018).**

Conclusion: **This study is providing good clinical observation in favour of high dose piracetam infusion to reduce the disability of the patients by improving their gait ataxia.**

***Keywords*: ataxia, autosomal dominant, cerebellar, piracetam, treatment**

INTRODUCTION

Autosomal dominant cerebellar ataxias (ADCA) are a group of hereditary neurodegenerative disorders known as spinocerebellar ataxias (SCA) in the genetic nomenclature (1). SCA display a wide range of neurological symptoms including ataxia of gait, stance and limbs; cerebellar dysarthria, and oculomotor disturbances of cerebellar and supranuclear origin. Retinopathy, optic atrophy, spasticity, peripheral neuropathy, sphincter disturbances, cognitive impairment and seizures are other neurological and systemic features of this heterogeneous group of hereditary disorders (1).

At present there is no known treatment to prevent the neuronal cell death or even to delay the age of onset of the ataxia. Current treatment is purely symptomatic; Parkinsonian features can be effectively treated with dopaminergic agents (2), amantadine is beneficial for dystonic movements and bradykinesia (3), and the treatment of tremor requires trial-and-error use of several drugs (1). However, ataxia remains the main therapeutic challenge in this disease. Trials with serotonin and buspirone have shown similarly mild clinical benefits (4, 5). Trimethoprim-sulfamethoxazole has been suggested for SCA type 3 but no effect could be detected in a large placebo-controlled trial (6). A previous case report suggesting benefit from administration of high dose piracetam stimulated the present study of the efficacy of this agent in patients with cerebellar ataxia (7).

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METHODS

Participants

Eight patients with cerebellar ataxia followed in a tertiary Movement Disorder Clinic were included in the study. All patients had clinically symptomatic ataxia and showed cerebellar atrophy on imaging studies. None of the patients had a known history of malignancy, alcohol abuse or toxin exposure. The protocol was approved by the Local Ethics Committee and all subjects provided written consent prior to enrolment according to the Declaration of Helsinki.

The genetic sequencing for SCA types 1, 2, 3, 6, 7, 8 and 17 was performed at the Kirac Foundation, Neurodegeneration Research Laboratory in Bogazici University.

Treatment and evaluation

All patients were given intravenous 30 g piracetam in 100 cc of 5% dextrose solution in three divided doses for 3 days. The dose was then increased to 45 g in 100 cc/day for another 3 days and to 60 g in 100 cc/day for the last 8 days (7). Subjects were allowed to continue all other medications. Pre- and post-infusion laboratory investigations included complete blood count, serum electrolytes, liver and renal function tests, and a lipid profile. The baseline and end-of-the study evaluations used the International Cooperative Ataxia Rating Scale (ICARS) for all subjects (8). Baseline scale was performed at admission and the scale was repeated at the end of the drug infusion period by the same examiner (D.B). ICARS is a clinician-rated, semiquantitative assessment of cerebellar impairment. The scale consists of four subscales contributing to a total ataxia score (maximum 100) including: posture and gait disturbances (items 1–7, score 0–34), kinetic functions (items 8–14, score 0–52), speech disorders (items 15 and 16, score 0–8) and oculomotor disorders (items 17–19, score 0–6).

The primary goal of the study was to determine the effect of high doses of piracetam infusion on cerebellar impairment as measured by ICARS, in subjects with cerebellar ataxia.

Statistical analyses were carried out using the Statistical Package for Social Sciences (SPSS, version 11·5; SPSS Inc., Chicago, IL, USA)-software. Statistical significance was determined using the Wilcoxon Signed Ranks test. Differences were considered significant for $P < 0{\cdot}05$.

RESULTS

Data from eight patients (mean age = 43·4 ± 14·2 years; mean disease duration = 10·38 ± 5·80 years) who had completed the entire protocol were included in the analysis. The demographic profiles and clinical features of the patients are shown in Table 1. Among all patients scanned for trinucleotide repeat sequencing, only case 6 was found positive for SCA 2. No side effects were observed during the study period and no laboratory changes were detected between pre- and post-infusion values. The mean total ICARS score was 39·4 ± 17·0 (range 9–60) at baseline and 30·9 ± 14·9 (range 8–55) after the piracetam infusion. Statistical analysis demonstrated a significant improvement in the patients' total score ($P = 0{\cdot}018$) and a subscale analysis showed statistical significance only for the posture and gait disturbances item ($P = 0{\cdot}018$). There was no evidence of an effect of piracetam infusion on other items of ICARS, including kinetic functions, speech and oculomotor disorders (Table 2).

DISCUSSION

The present report investigated the role of high dose (60 g daily) piracetam in patients with ADCA and demonstrated a significant improvement mainly in the posture and gait disturbances item of ICARS.

Piracetam (2-oxo-1-pyrrolidine-acetamide) is a low molecular weight derivative of γ-aminobutyric acid. When tested for several neurotransmitter receptors in the central nervous system, piracetam shows relative specificity for ^{3}H-glutamate sites. Intrinsic connections in the motor cortex use glutamate as excitatory neurotransmitter acting via *N*-methyl-D-asparate (NMDA) or non-NMDA receptors (9). A recent study of the motor cortex has shown that the probable glutamatergic activity of piracetam may potentially be the mechanism of action in cortical myoclonus for which it has proved to be a highly efficacious treatment (10). Although the mode of action of piracetam in the nervous system is not well-defined, its efficacy has been documented in a wide range of clinical indications

Table 1. Demographic and clinical manifestations of ADCA patients

	Age	Disease duration (years)	Clinical phenotype	Clinical manifestations	MRI	SPECT
Case I[a]	35/M	9	ADCA I	Myoclonus	Cerebral-cerebellar atrophy	NA
Case II[a]	50/F	20	ADCA I	PNP	Cerebral-cerebellar atrophy	NA
Case III	70/F	15	ADCA I	PNP	Cerebellar atrophy	NA
Case IV	52/M	15	ADCA I	Myoclonus, Extrapyramidal symptoms	Cerebral-cerebellar atrophy	Cerebellar hypoperfusion
Case V	42/F	7	ADCA I	PNP	Cerebellar atrophy	Cerebellar hypoperfusion
Case VI[b]	26/F	8	ADCA I	PNP	Cerebellar atrophy	NA
Case VII	29/F	7	ADCA III	–	Cerebellar atrophy	NA
Case VIII	43/F	2	ADCA III	–	Cerebellar atrophy	NA

NA, not available; PNP, polyneuropathy; ADCA, Autosomal dominant cerebellar ataxia.
[a]Siblings.
[b]Genotype: SCA-2.

Table 2. Baseline and post-infusion evaluation of study patients by ICARS

ICARS compartments	Mean ± SD (range)	*P*-value
Posture and gait		
Baseline	17·9 ± 8·7 (2–29)	**0·018**[a]
Post-infusion	13·7 ± 9·2 (0–29)	
Kinetic functions		
Baseline	17·0 ± 11·5 (5–42)	0·104
Post-infusion	13·4 ± 8·0 (6–30)	
Speech disorders		
Baseline	3·6 ± 1·3 (2–5)	0·102
Post-infusion	2·6 ± 0·9 (1–4)	
Oculomotor disorders		
Baseline	1·0 ± 1·4 (0–4)	1·000
Post-infusion	1·0 ± 1·4 (0–4)	
Total score		
Baseline	39·4 ± 17·0 (9–60)	**0·018**[a]
Post-infusion	30·9 ± 14·9 (8–55)	

ICARS, International Co-operative Ataxia Rating Scale.
[a]Statistically significant.

like cognitive disorders and dementia, vertigo and dyslexia as well as cortical myoclonus (9).

Piracetam is generally well tolerated even at high doses, although slight elevations in serum creatinine levels have been reported (7). Additional cumulative doses would carry the risk of more severe side effects and may probably be a limiting factor in the elderly. Therefore, an extensive laboratory screening was performed in all patients as to serum electrolytes, liver and renal function tests, and no changes were observed during the study period.

To evaluate the efficacy of symptomatic treatment, appropriate clinical scales are required. To this purpose, ICARS was developed and published in 1997 to evaluate cerebellar impairment (8). This scale not only quantifies ataxia comprehensively, but also allows measurement of different components of ataxia (11). ICARS is divided into four subscales that measure posture and gait disturbances, kinetic functions, speech disorders and oculomotor disorders. ADCAs are progressive disorders and the rate of progression is variable depending on the genotype. A moderate correlation was demonstrated between ICARS score and disease duration justifying the use of this scale in clinical trials. In the present study, ataxia was evaluated by ICARS before and after piracetam infusions and a statistically significant ($P = 0{\cdot}018$) improvement in the total ataxia score was detected. Subscale analyses demonstrated a significant difference only in the 'posture and gait' item ($P = 0{\cdot}018$). This subscale evaluates impairment in walking, speed of gait, standing, body sway and quality of sitting. The second subscale, named 'kinetic functions', mainly tests the disability related to extremity ataxia and tremor including the drawing of the Archimedes's spiral. The other

two subscales measure the impairment caused by dysarthria and oculomotor signs like nystagmus, abnormalities of ocular pursuit and saccades.

As a conclusion, the data analysis of this study showed that high doses of piracetam are mainly effective in gait ataxia, but the small number of patients prevented further detailed subgroup analysis. The present study reinforces the thesis of a potential anti-ataxic effect of piracetam in cerebellar disorders although the open-label design and lack of placebo controls are limitations. Nevertheless, this study is providing a good clinical observation in favour of high doses piracetam infusions to reduce the disability of ADCA patients by improving their gait ataxia. Gait analysis studies seem to be necessary to confirm the efficacy of piracetam in this group of disabling degenerative disorders.

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