Original Article

Nerve Growth Factor for the Treatment of Spinocerebellar Ataxia Type 3: An Open-label Study

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Abstract

Background: Spinocerebellar ataxia type 3 (SCA3) is the most common subtype of SCA worldwide, and runs a slowly progressive and unremitting disease course. There is currently no curable treatment available. Growing evidence has suggested that nerve growth factor (NGF) may have therapeutic effects in neurodegenerative diseases, and possibly also in SCA3. The objective of this study was to test the efficacy of NGF in SCA3 patients.

Methods: We performed an open-label prospective study in genetically confirmed adult (>18 years old) SCA3 patients. NGF was administered by intramuscular injection (18 μg once daily) for 28 days consecutively. All the patients were evaluated at baseline and 2 and 4 weeks after treatment using the Chinese version of the scale for assessment and rating of ataxia (SARA).

Results: Twenty-one SCA3 patients (10 men and 11 women, mean age 39.14 ± 7.81 years, mean disease duration 4.14 ± 1.90 years, mean CAG repeats number 77.57 ± 2.27) were enrolled. After 28 days of NGF treatment, the mean total SARA score decreased significantly from a baseline of 8.48 ± 2.40 to 6.30 ± 1.87 ($P < 0.001$). Subsections SARA scores also showed significant improvements in stance ($P = 0.003$), speech ($P = 0.023$), finger chase ($P = 0.015$), fast alternating hand movements ($P = 0.009$), and heel-shin slide ($P = 0.001$).

Conclusions: Our preliminary data suggest that NGF may be effective in treating patients with SCA3.

Key words: Nerve Growth Factor; Open-label Study; Spinocerebellar Ataxia Type 3; Scale for Assessment and Rating of Ataxia

Introduction

Spinocerebellar ataxia type 3 (SCA3), also known as Machado–Joseph disease, is the most common subtype of SCA world-wide,[1,2] and is caused by a pathologic CAG trinucleotide repeat expansion in the *ATXN3* gene located on chromosome 14q32.12.[3,4] The cardinal clinical characteristics of SCA3 include gait and stance unsteadiness, limb ataxia, dysarthria, oculomotor dysfunction, sensory disorder, pyramidal and extrapyramidal dysfunction, and so on.[1,5] SCA3 is a slowly progressive and unremitting disease,[6-8] in which patients generally will become wheelchair-bound and bedridden in the end stage, and the median survival time after disease onset is approximately 21 years.[9] The resulting loss of working ability and reduced survival confer significant disease burden to the patients, their families, and the society. So far, effective treatment measures for this disease are still lacking.[10-13] Thus, it is of vital importance to explore effective therapeutic options in order to alleviate the symptoms or retard the disease progression in SCA3.

Nerve growth factor (NGF) is the founding member of the neurotrophin family,[14] and is essential for the proper development, patterning, and maintenance of the mammalian nervous system.[15] Previous studies have revealed that NGF specifically targets sensory and sympathetic neurons in the peripheral nervous system, as well as basal forebrain cholinergic neurons in the central nervous system.[16,17] There is also growing evidence to support the role of NGF in the development, differentiation, and maintenance of the human cerebellar connectivity. In this context, NGF and its high-affinity receptor tachykinin receptor antagonist (TkrA) have been found on the human cerebellar neurons and their neurites.[18,19] These data imply that NGF may have neuroprotective effects on cerebellar neurons and hence might serve as a therapeutic candidate of SCA3. Therefore, this clinical pilot study was set forth to examine the efficacy of NGF in patients with SCA3.

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Methods

This study was an open-label clinical trial assessing the efficacy of NGF in patients with SCA3; it was conducted at the First Affiliated Hospital of Zhengzhou University from November 2011 to November 2012. This study was approved by the Ethics Committee of First Affiliated Hospital of Zhengzhou University and registered at the Chinese Clinical Trial Registry (www.chictr.org; ChiCTR-ONC-11001954). All study procedures were in accordance with the declaration of Helsinki and all recruited subjects have provided written informed consents.

Ataxia patients with family history were screened at the Department of Neurology, First Affiliated Hospital of Zhengzhou University and referred for genetic testing at the Department of Genetic Diagnosis. Patients who fulfilled the following inclusion criteria: (1) ataxia patients with family history were checked and diagnosed by two independent doctors, then the genotype SCA3 was confirmed by genetic test; (2) older than 18 years; and (3) willing to give informed consent, will be recruited. The exclusion criteria were as follows: (1) allergy to neurotrophin; (2) with concomitant severe systematic diseases or psychiatric disorders; (3) unable to finish the scale for assessment and rating of ataxia (SARA) score; (4) refuse to attend the study, and (5) ataxias attributed to secondary causes (such as alcohol or drug abuse and toxic exposure). All enrolled patients underwent standard neurological, electrophysiological and neuroimaging examinations, and the SCA3 subtype was classified according to these clinical findings.[20]

Murine derived NGF (mNGF) (Xiamen Bioway Biotech Co., Ltd. China) used in this study was extracted and purified from the submandibular gland of the male mouse and has high homology in the amino acid sequence with human NGF.[21] The mNGF has been safely used in a series of clinical studies.,[22,23] and has been approved by China Food and Drug Administration. mNGF was administered peripherally by intramuscular injection at the dose of 18 μg once daily for 4 weeks consecutively.

Clinical disease severity was assessed by the Chinese version of SARA.[24,25] It has been proven to have good reliability and validity among Chinese patients with degenerative cerebellar. The SARA evaluates axial (gait, stance, sitting), speech, and appendicular (finger chase, nose-finger test, fast alternating hand movements (FAHMs), and heel-shin slide) functions. The SARA sum score ranges from 0 to 40 with 0 indicating no ataxia and 40 the most severe ataxia, thus deterioration or improvement of disease severity is, respectively, represented by an increase or decrease of the SARA score. For each patient, Chinese version of SARA was performed at the baseline, 2 weeks (midpoint) and 4 weeks (endpoint) after treatment. These SARA evaluations were all videotaped and reviewed independently by two other investigators who did not attend the original assessment in a random order. The average of score rated by these two evaluators was denoted as the final SARA score. The primary outcome measure was the change of SARA score after treatment compared with that at baseline.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were expressed as frequencies or proportions where appropriate. The observed changes of SARA score after treatment from baseline were analyzed with nonparametric Wilcoxon signed-rank test. A $P < 0.05$ was considered to be statistically significant. All the analyses were performed using the SPSS Statistical Package 17.0 (SPSS Inc., USA).

Results

Twenty-one patients with genetically confirmed SCA3 were enrolled in this study. The baseline clinical characteristics of these patients were presented in Table 1. There were 10 men (47.6%) and 11 women (52.4%). The mean age was 39.14 ± 7.81 years, the mean age of onset was 35.00 ± 6.53 years, the mean disease duration was 4.14 ± 1.90 years, and the mean CAG repeats number was 77.57 ± 2.27.

The mean SARA score dropped from 8.48 ± 2.40 to 6.94 ± 2.34 ($P < 0.001$) and 6.30 ± 1.87 ($P < 0.001$) after 2 and 4 weeks of treatment, respectively [Table 2]. Significant decrease in subsections SARA scores was also observed in stance ($P = 0.008$ and 0.003), speech ($P = 0.046$ and 0.023), finger-chase ($P = 0.026$ and 0.015), FAHMs (0.015 and 0.009), and heel-shin slide ($P = 0.006$ and 0.001) at 2 and 4 weeks after therapy, respectively. The mean improvement in total SARA score was 2.18 ± 1.30 (ranging from 0 to 5.75) in our study.

Discussion

Currently, there are few effective measures for treatment of SCA3.[26,27] One previous study has shown that insulin-like growth factor-1, one of the neurotrophic factors, may be effective in reducing the disease progression of SCA3.[28] Previous studies have reported that NGF can improve cognitive decline in patients with Alzheimer's disease and may also have potential therapeutic roles in other neurodegenerative diseases.[29-31] Postmortem histopathological study in patients with SCA3 has revealed considerable neuronal loss at the cerebellar Purkinje cell layer and the four deep cerebellar nuclei.[32] NGF can prevent neuronal death or age-related atrophy in the adult brain by inhibiting apoptosis of cholinergic neurons in the basal forebrain,[33] and it would be reasonable to postulate that it may also inhibit the apoptosis in the cerebellum neurons expressing tyrosine kinase A (TrkA) and serve as a potential therapy for SCA3.

Our current pilot data suggest that NGF might be an effective treatment for SCA3. Such treatment effect is observed as early as 2 weeks after therapy and sustained after 4 weeks. To our knowledge, this study is the first to investigate the efficacy of NGF in SCA3. We postulate such therapeutic effects might be mediated by two mechanisms. First, peripheral administration

Table 1: Baseline clinical characteristics of 21 SCA3 patients

Patient number	Gender	Age (years)	Age at onset (years)	Duration (years)	Peripheral neuropathy	Pyramidal signs	Cerebellar atrophy	CAG repeats number
1	Male	31	27	4	No	Yes	No	81
2	Male	43	38	5	Yes	No	Yes	77
3	Female	53	43	10	Yes	No	Yes	75
4	Male	39	34	5	No	Yes	No	77
5	Female	46	42	4	Yes	No	Yes	78
6	Female	39	36	3	No	Yes	Yes	77
7	Male	30	28	2	No	Yes	Yes	80
8	Female	25	23	2	No	Yes	No	82
9	Male	22	21	1	No	Yes	No	82
10	Male	37	33	4	No	No	No	79
11	Female	35	32	3	Yes	Yes	Yes	78
12	Female	47	41	6	No	Yes	No	76
13	Male	41	38	3	Yes	Yes	Yes	76
14	Female	38	33	5	No	Yes	No	77
15	Male	44	38	6	No	Yes	Yes	75
16	Male	31	28	3	No	Yes	Yes	79
17	Female	44	41	3	No	Yes	Yes	74
18	Female	45	40	5	No	Yes	No	76
19	Female	43	38	5	No	Yes	Yes	78
20	Female	47	44	3	No	Yes	No	75
21	Male	42	37	5	Yes	No	Yes	77

SCA3: Spinocerebellar ataxia type 3.

Table 2: Scores of SARA and its subsections at baseline, 2 and 4 weeks after NGF therapy

SARA score	Baseline	Midpoint (2-week)	Endpoint (4-week)	P_1*	P_2†
Total	8.48 ± 2.40	6.94 ± 2.34	6.30 ± 1.87	<0.001	<0.001
Gait	2.38 ± 0.52	2.21 ± 0.56	2.26 ± 0.49	0.149	0.102
Stance	2.29 ± 0.46	1.81 ± 0.60	1.60 ± 0.80	0.008	0.003
Sitting	0.02 ± 0.11	0.02 ± 0.11	0.00 ± 0.00	1.000	0.317
Speech	0.69 ± 0.60	0.60 ± 0.54	0.50 ± 0.47	0.046	0.023
Finger chase	0.37 ± 0.50	0.23 ± 0.37	0.18 ± 0.25	0.026	0.015
Nose-finger test	0.05 ± 0.22	0.04 ± 0.12	0.00 ± 0.00	0.655	0.317
FAHM	1.51 ± 1.07	1.12 ± 0.88	1.07 ± 0.93	0.015	0.009
Heel-shin slide	1.19 ± 0.58	0.88 ± 0.42	0.69 ± 0.40	0.006	0.001

*Comparisons between midpoint of therapy and baseline; †Comparisons between endpoint of therapy and baseline. SARA: Scale of the assessment of rating of ataxia; FAHM: Fast alternating hand movements; NGF: Nerve growth factor.

of NGF may have a direct effect on the cerebellum. Postmortem study has shown that NGF and its high-affinity receptor TkrA are distributed in the neurons of the human cerebellum cortex and its deep nuclei throughout life.[18,19] These findings support the involvement of NGF in the development, differentiation and maintenance of the cerebellar connectivity. Although the blood-brain barrier (BBB) has low permeability to large proteins, some autoradiography studies suggested ED that blood-borne NGF and its subunit β-NGF can cross the BBB of mice and arrive at the brain parenchyma by direct permeation.[34,35] Second, the therapeutic effect of NGF might also be mediated via the proprioceptive sensation system. It has been reported that most (87%) of the SCA3 patients had somatosensory evoked potential abnormalities, especially in the lower limbs, which was due to degenerative lesions in the dorsal column of the spinal cord.[36,37] TrkA immunoreactive fibers have been found in the dorsal column of rats.[38] Hence, NGF therapy may improve stance and heel-knee-shin slide due to improved proprioception. These two proposed mechanisms may explain the observed improvement after therapy and substantiate the use NGF to treat a patient with SCA3.

Our study had several limitations. First, it was an open-label study, in which the observed therapeutic efficacy might be contributed by placebo effects. However, in one randomized, double-blind, and placebo-controlled study to evaluate the efficacy of varenicline in SCA3 patients, the mean improvements of SARA score in the therapeutic group, and the placebo group were 1.97 and 0.86, respectively.[12] The SARA score improvement of 2.18 in our current study is unlikely to be accounted for by placebo effect alone. Furthermore, SARA is a reliable and valid scale to linearly assess the ataxia symptoms, and changes of SARA scores exceeding 1.1 points are considered clinically relevant.[39] Other limitations include the small sample and short duration of follow-up. Nevertheless, our pilot data suggest that NGF may be a promising treatment for patients with SCA3. A large-scale randomized, double-blind placebo-controlled trial would be worthwhile to evaluate the efficacy and tolerability of NGF in SCA3 patients.

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