

# Neurological Recovery with Interferon-gamma Treatment in Friedreich's Ataxia

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## ABSTRACT

Friedreich's ataxia (FA) is a rare, progressive, and degenerative hereditary disorder caused by a deficiency of frataxin protein. This disease is characterised by severe neurological dysfunction and life-threatening cardiomyopathy. Various drugs are used to slow down / stop the neurodegenerative progress. However, recent clinical trials and animal experiments demonstrate that interferon-gamma (IFN- $\gamma$ ) treatment might improve signs of FA as well.

A 9-year-old girl was admitted to our hospital with gait instability, mild dysarthria, and sensorimotor polyneuropathy. Her genetic examination was consistent with FA. IFN- $\gamma$  treatment was started 3 times a week.

The treatment was evaluated by physical examination and side effects assessment. Friedreich Ataxia Rating Scale (FARS), 9-hole peg test (9HPT), and time of 25-foot walk (T25FW) were measured. Ataxia and cerebellar findings improved within 9 months. Although clinical neurological improvement was achieved, there was no improvement in cardiomyopathy.

**Key Words:** Interferon-gamma, Friedreich ataxia, FARS, Children, Cardiomyopathy.

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## INTRODUCTION

Friedreich's ataxia (FA) is an autosomal recessive disease that causes life-threatening system damages such as neurodegeneration, cardiomyopathy, diabetes mellitus, along with functional effects such as progressive ataxia, hearing, and vision loss. The severity of illness depends on frataxin levels. There are few studies aimed at reducing mitochondrial damage by increasing frataxin levels in the literature.<sup>1</sup>

Interferon-gamma (IFN- $\gamma$ ) is an endogenous cytokine that takes part in the immune response to viral infections. Several studies in mouse models showed that the usage of IFN- $\gamma$  could increase the frataxin levels, and hence mobility.<sup>2</sup>

In recent studies with few patients, the Friedreich Ataxia Rating Scale (FARS) was improved with IFN- $\gamma$  treatment. Based on these studies, we aim to present a patient who has been given human recombinant IFN- $\gamma$  1b (IMUKIN®) for the treatment of FA.

## CASE REPORT

A 9-year girl, born of a second-degree relative marriage, was admitted to our hospital with complaints of ataxia and impaired fine motor skills, which have been noted for almost 1.5 years.

On neurological examination, cranial nerves were normal, muscle strength and tone were normal, but Achilles and patellar reflexes were absent. Bilateral pes cavus and hammer toe were present. She described tingling in the finger-to-finger and nose-finger tests. The vibratory and position sense of toes were also impaired. She had no hearing or sight complaints but showed mild dysarthria and dysmetria. Swallowing and feeding were normal. There were no involuntary movements and calf muscle hypertrophy. Incompetency was observed while she was cutting food or using scissors. Electromyography (EMG) revealed sensorimotor polyneuropathy. Nerve conduction velocity was decreased, especially at the lower extremities. Cranial and spinal magnetic resonance images were normal. Left ventricular hypertrophy without prolonged QRS duration and inversion of T waves in left chest leads were revealed with the electrocardiogram (ECG). In echocardiogram (ECO), hypertrophic cardiomyopathy and minimal left ventricular hypertrophy were observed. The ejection fraction was normal. Septum thickness was 14 mm. However, the patient did not have any cardiac symptoms. Metoprolol was started at 1 mg/kg for cardiomyopathy.

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**Table I: Monitoring tests at baseline and during treatment with IFN- $\gamma$ .**

	Baseline	112 days	280 days
FARS	37	33	31
9HPT (right/left)	16,42/17.23 sec	16.25/17.02 sec	16.45/17.19 sec
T25FW	14.9 sec	14.6 sec	14.7 sec
ECO	septum thickness 14 mm	septum thickness 14 mm	septum thickness 16 mm
Audiometry	20 db/20 db	20 db/20 db	16 db/16 db

FARS: Friedreich ataxia rating scale; 9HPT: 9-hole peg test; T25FW: 25-foot walk; ECO: Echocardiogram.

Since the patient was clinically compatible with FA, physiotherapy was initiated. Blood samples were sent for the number of GAA repeats, and the number of expansions was found to be above 66 copies in both alleles. Co-enzyme Q and idebenone treatments were initiated, and IFN- $\gamma$  treatment was started as soon as the permission was obtained from the Health Ministry.

Clinical and laboratory follow-up was performed for 9 months. An informed consent was obtained from the patient and the family. Ethics committee approval was granted for this study (2019-07-212664).

The baseline FARS, ECO, physical examination, 9-hole peg test (9HPT), and 25-foot walk (T25FW) measurements were performed. IFN- $\gamma$  was administered for the first 14 days at a dose of 10  $\mu\text{g}/\text{m}^2$  3 days/week, followed by 14 days at 25  $\mu\text{g}/\text{m}^2$  3 days/week and then 50  $\mu\text{g}/\text{m}^2$  3 days/week. The patient was evaluated with the physical examination, side effects, complaints, FARS, 9HPT, T25FW, audiometry, and ECO on days 112<sup>th</sup> and 280<sup>th</sup> after starting IFN- $\gamma$  treatment (Table I).

Flu-like symptoms (without fever) were seen during treatment. On the 112<sup>th</sup> day, improvement in the upper extremity movements was observed. On the 280<sup>th</sup> day, walking and scissoring skills were significantly improved, and ataxia was almost recovered. Handwriting improved considerably compared to before treatment. Minimal cardiological deterioration was observed.

## DISCUSSION

GAA triplet repetition leads to impaired synthesis of the frataxin protein. Decreased levels of frataxin cause mitochondrial respiratory activity reduction, and mitochondrial iron overload, which leads to free radical accumulation within the cells. It has been shown that IFN- $\gamma$  controls iron use and prevents iron stores from being used by pathogens. Therefore, it is thought that IFN- $\gamma$  could regulate frataxin.<sup>2</sup>

Coenzyme Q and idebenone have been used in the treatment of FA for many years. However, even if this treatment slows down the progress of FA, there is not enough evidence to show that it can stop the progression of the disease.

Seyer *et al.* showed that IFN- $\gamma$  treatment can be beneficial and has no side effects. In their study, a 5-point decrease was observed in FARS scores with IFN- $\gamma$  treatment at 3

months, while a 5-point increase was observed at 18 months in those who did not receive treatment.<sup>3</sup> Lynch *et al.* found no difference in FARS scores on comparing placebo with IFN for 6 months. However, after the results were announced, FARS values (4 points) were much better in those who remained on active treatment than the ones who discontinued.<sup>4</sup> Therefore, it may be recommended to continue the treatment in patients who believe they benefit clinically, even if they do not benefit statistically. The present patient showed a 4-point decrease in FARS at 7-month and a 6-point decrease at 9-month follow-up with IFN treatment. Therefore, the improvement in this patient is considered to be quite satisfactory.<sup>5</sup> The loss of coordination was more prominent (compared with initial locomotor loss) in this patient and the improvement was significant in this symptom. In the first evaluation, improvement in dysmetria was observed. Moreover, subsequent evaluations also showed further improvement in hand, hand skills, and coordination. Despite the patient's increased mobility with the improvement of ataxia, no cardiac symptoms were noted. However, there was no improvement in heart wall thickness.

This patient clearly benefited from IFN- $\gamma$  treatment; therefore, we continued the treatment. The effects of neurological improvement on the quality of life cannot be denied. Besides, there have been no critical side effects of IFN usage reported so far.

In conclusion, the clinical neurological improvement in the present case underscores the need for larger, multinational, randomised controlled trials to confirm the clinical benefits of IFN in FA.

### PATIENT'S CONSENT:

Consent was obtained from the patient and her family for the publication of this article.

### COMPETING INTEREST:

The authors declared no conflict of interest.

### AUTHORS' CONTRIBUTION:

HGT: Conception and design, interpretation, data acquisition and analysis, drafting, final approval.

EL: Interpretation, critical revision, final approval.

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