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TOFACITINIB IMPROVES MOTOR SYMPTOMS IN PARKINSONISM ASSOCIATED WITH A HETEROZYGOUS NGLY1 VARIANT AND AUTOIMMUNE DISEASE

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ABSTRACT

Introduction: Levodopa-refractory parkinsonism poses a significant diagnostic and therapeutic challenge. Variants in N-glycanase 1 (NGLY1), a key gene in proteostasis, have been associated with movement disorders, and the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway is implicated in neuroinflammation.

Case description: We report a 59-year-old woman with parkinsonism and autoimmune polyendocrine syndrome type III, carrying a heterozygous pathogenic NGLY1 variant (p.Arg401Ter). Her motor symptoms were unresponsive to multiple dopaminergic therapies, and a formal levodopa challenge test was negative.

Treatment with the JAK inhibitor tofacitinib (5 mg twice daily), initiated for seronegative arthritis, was associated with sustained improvement in rigidity and gait freezing, paralleled by remission of her autoimmune manifestations. Temporary discontinuation of tofacitinib coincided with clinical worsening, followed by recovery upon reintroduction.

Discussion: The temporal association between JAK inhibition and motor improvement suggests that modulation of systemic inflammation may influence neurological outcomes in selected patients. A heterozygous NGLY1 variant could act as a disease modifier through neuroimmune dysregulation.

Conclusions: This observation highlights a potential link between immune activation and parkinsonian symptoms in patients with systemic autoimmune disease. Immunomodulatory therapy may represent an adjunctive consideration in complex neuroinflammatory presentations, warranting further investigation.

KEYWORDS

Parkinson's disease, NGLY1 variant, autoimmune polyendocrine syndrome type III (APS-3), tofacitinib, neuroinflammation

LEARNING POINTS

- Tofacitinib, a Janus kinase inhibitor, was associated with clinical improvement of parkinsonian symptoms in a patient with systemic autoimmune disease, suggesting a potential modulatory role of inflammation in refractory movement disorders.
- The presence of a heterozygous N-glycanase 1 variant may contribute to susceptibility or clinical expression of parkinsonism in the setting of immune or inflammatory dysregulation.
- This case underscores the interplay between immunological and neurodegenerative mechanisms when facing atypical or treatment-refractory neurological presentations.

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INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta, leading to bradykinesia, tremor, rigidity, and postural instability. Although most PD cases are sporadic, genetic factors play an important role in familial forms, with pathogenic variants in SNCA, LRRK2, and PARK2 firmly established in disease pathogenesis[1]. Impairment of the cellular proteostasis network, which governs protein folding and degradation, results in the accumulation of misfolded proteins—a central mechanism in PD. Within this network, the endoplasmic reticulum–associated degradation (ERAD) pathway, where the N-glycanase 1 (NGLY1) enzyme operates, is critical for maintaining protein homeostasis[1–4].

The NGLY1 gene encodes a cytosolic deglycosylase that removes N-linked glycans from misfolded glycoproteins. Loss-of-function mutations in NGLY1 cause a congenital disorder of deglycosylation (OMIM #615273), typically due to biallelic variants and transmitted in an autosomal recessive pattern[2]. Although heterozygous truncating variants are not classically pathogenic, they may contribute to disease susceptibility via haploinsufficiency or modifier effects. Indeed, NGLY1 variants have been associated with hyperkinetic movement disorders, suggesting that even partial impairment of enzymatic function can alter neuronal proteostasis[2–4]. While a direct link between NGLY1 variants and parkinsonism has not been reported, their role in cellular stress and mitochondrial dysfunction provides a plausible mechanistic connection.

Autoimmune polyendocrine syndrome type III (APS-3) is defined by the coexistence of autoimmune endocrine and musculoskeletal diseases such as celiac disease, Hashimoto's thyroiditis, seronegative arthritis, and vitiligo. This constellation reflects a state of chronic systemic inflammation, which may contribute to the neuroinflammatory environment implicated in neurodegenerative disorders, including PD[4–6]. Although specific treatments for APS-3 are lacking, its inflammatory burden supports investigation into targeted immunomodulatory approaches.

Recent observations in autoimmune polyendocrine syndrome type I (APS-1) have demonstrated that Janus kinase (JAK) inhibitors can attenuate interferon-mediated inflammation[6,7]. Despite immunopathological differences between APS-1 and APS-3, these findings suggest that JAK inhibition may also mitigate systemic inflammation in APS-3, particularly in patients with concomitant neurodegenerative processes.

In this context, we describe a patient with PD associated with a heterozygous truncating NGLY1 mutation (p.Arg401Ter), seronegative arthritis, and APS-3, whose neurological and autoimmune manifestations improved during treatment with the JAK inhibitor tofacitinib.

CASE DESCRIPTION

A 59-year-old woman, diagnosed with PD at age 53 after presenting with a left-hand resting tremor, progressively developed bradykinesia, rigidity, and episodes of freezing gait. Non-motor symptoms included hypophonia and vivid dreams, though polysomnography showed no rapid eye movement sleep disturbance; she did not report hyposmia. Motor symptoms were refractory to multiple dopaminergic agents (pramipexole, ropinirole, trihexyphenidyl, levodopa/carbidopa, rasagiline, safinamide, and rotigotine). Pramipexole was discontinued due to hallucinations and oedema, while levodopa induced paradoxical dystonia of the left leg at doses as low as 50 mg. Continuous subcutaneous apomorphine infusion was stopped because of hypotension, dyskinesia, and dystonia. Botulinum toxin injections produced only partial tremor reduction (~20%) and transient paresis. A formal levodopa challenge (200 mg) showed no improvement (MDS-UPDRS Part III: 40 OFF vs 40 ON) and triggered further dystonia *(Fig. 1)*.

Her medical history included APS-3, consisting of celiac disease, Hashimoto's thyroiditis, seronegative arthritis, and vitiligo. Family history revealed clustering of autoimmune and neurological disorders: her father had parkinsonism in his sixth decade; a maternal cousin was diagnosed with multiple system atrophy; her brother had APS-3; and both her mother and son had autoimmune thyroid disease.

Given the complex phenotype and autoimmune background, genetic testing was performed. A next-generation

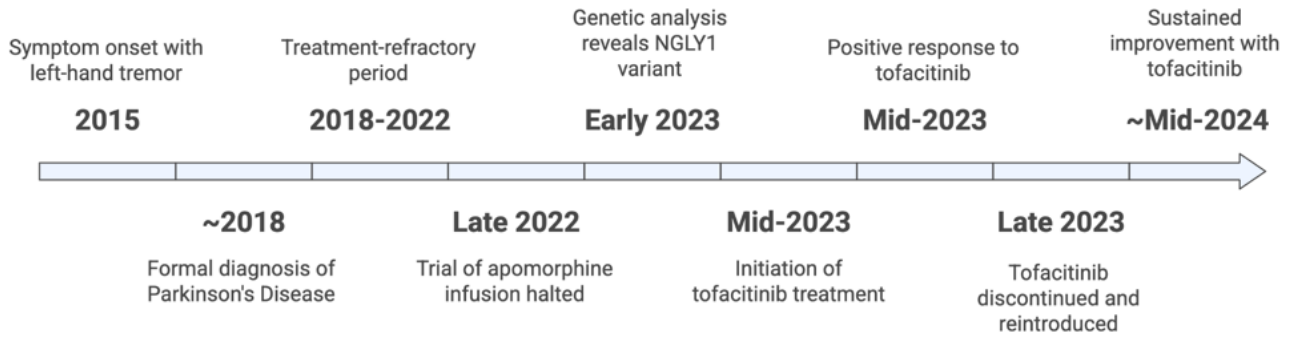


Figure 1. Timeline of key clinical events. Chronological summary of the patient's clinical course from initial symptom onset in 2015 to sustained improvement in mid-2024. The figure illustrates the progression from left-hand tremor and diagnosis of Parkinson's disease, through a prolonged treatment-refractory period, identification of the heterozygous N-glycanase 1 (NGLY1) variant, initiation of tofacitinib therapy, and the subsequent clinical improvement following reintroduction of treatment after a temporary interruption.

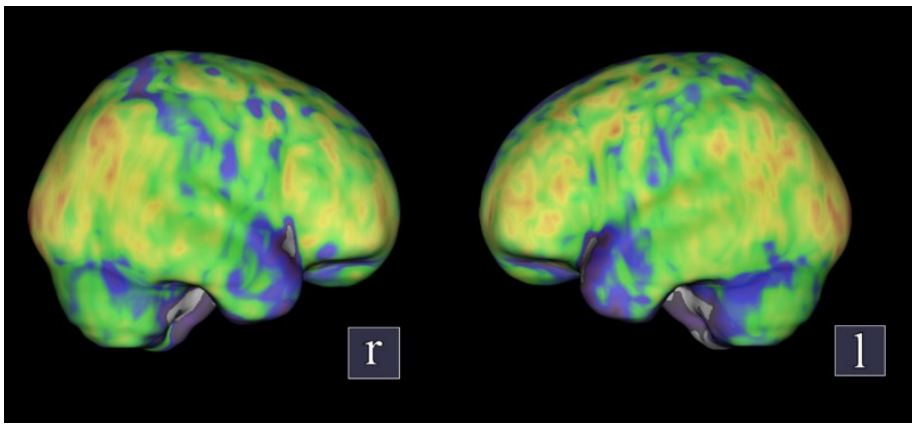


Figure 2. Mild bilateral antero-mesial temporal cortical hypometabolism in PET scan. Small diffuse areas of mild–moderate hypometabolism related to cortical atrophy, predominantly affecting the bilateral antero-mesial temporal cortex.

sequencing panel for early-onset parkinsonism (ATP13A2, DNAJC6, FBXO7, LRRK2, PINK1, PRKN, SNCA, SYNJ1, VPS13C, VPS35, and GBA1) was negative. Extended analysis revealed a heterozygous pathogenic nonsense variant in exon 8 of NGLY1 (c.1201A>T; p.Arg401Ter), classified as "likely pathogenic" by American College of Medical Genetics and Genomics criteria and absent from population databases such as gnomAD.

Neurological examination showed marked hypomimia (grade 3), moderate resting tremor in the left hand (grade 2), and mild-to-moderate rigidity, greater on the left (upper limbs grade 3 vs 2; lower limbs grade 2 vs 1; axial rigidity grade 3). Bradykinesia was evident in all limbs, more pronounced on the left. Gait evaluation revealed normal stride length but reduced left arm swing and persistent tremor during ambulation. The pull test was positive for retropulsion, without dystonia or dyskinesias.

Laboratory results demonstrated mild leukopenia (3,570/µl) with neutropenia (2,110/µl), positive antinuclear antibodies (1:160, speckled), and elevated anti-thyroid peroxidase antibodies (59.1 IU/ml). All other autoantibodies, including extractable nuclear antigens, antiphospholipid, and antineuronal antibodies, were negative. Brain magnetic resonance imaging was unremarkable. Dopamine transporter scan (DaTscan) showed bilateral presynaptic dopaminergic deficits, more pronounced on the right. Myocardial meta-iodobenzylguanidine scintigraphy revealed reduced late-phase uptake with increased washout. Brain positron emission tomography demonstrated mild bilateral anteromesial temporal cortical hypometabolism with preserved basal ganglia metabolism *(Fig. 2)*.

She was referred to the Systemic Immune-Mediated Diseases Unit for management of seronegative arthritis and APS-3 in the context of levodopa-refractory PD. Previous treatment with hydroxychloroquine and methylprednisolone was ineffective, and other immunosuppressants were poorly tolerated. Considering the inflammatory background, prior reports of JAK inhibition in APS[6,7], and tofacitinib's ability to cross the blood–brain barrier and modulate interferon-related signalling, tofacitinib 5 mg twice daily was initiated.

Within weeks, she experienced substantial improvement in joint pain, stiffness, and mobility, accompanied by subjective and objective improvement in motor function, including decreased rigidity and fewer freezing episodes. Rigidity improved to grade 2 in the left upper limb and grade 1 in the left lower limb.

Tofacitinib was temporarily discontinued for 1 month due to suspected gastrointestinal symptoms, later deemed unrelated. During the interruption, motor symptoms worsened markedly, with reappearance of rigidity and gait freezing. Upon reintroduction, both neurological and musculoskeletal benefits recurred.

After more than 10 months of continuous tofacitinib therapy, PD symptoms remain stable with sustained motor improvement, arthritis is in remission, and APS-3 manifestations are well controlled.

DISCUSSION

PD is increasingly recognized as a multifactorial disorder in which impaired proteostasis and chronic neuroinflammation complement classical dopaminergic neurodegeneration. Disruption of the ERAD pathway contributes to endoplasmic reticulum stress and mitochondrial dysfunction—mechanisms known to exacerbate neuronal vulnerability in PD[2,3].

NGLY1 encodes a cytosolic deglycosylase that removes N-linked glycans from misfolded glycoproteins, facilitating proteasomal degradation. The heterozygous nonsense variant p.Arg401Ter identified in this patient is predicted to cause nonsense-mediated messenger ribonucleic acid decay or result in a truncated, nonfunctional protein. Although NGLY1-related disorders are classically associated with biallelic mutations, it is conceivable that a heterozygous variant may act as a disease modifier, particularly under conditions of chronic inflammation or immune activation. Experimental data support the pathogenic potential of such variants through impaired protein clearance, cellular stress, and dysregulated innate immunity[2,3].

Impaired NGLY1 activity may activate intracellular sensors such as melanoma differentiation–associated protein 5 (MDA5), leading to stimulation of the Janus kinase/ signal transducer and activator of transcription (JAK/STAT) pathway and increased production of type I interferons and proinflammatory cytokines *(Fig. 3)*. This cascade can promote microglial activation and dopaminergic neuron loss, establishing a mechanistic link between proteostatic

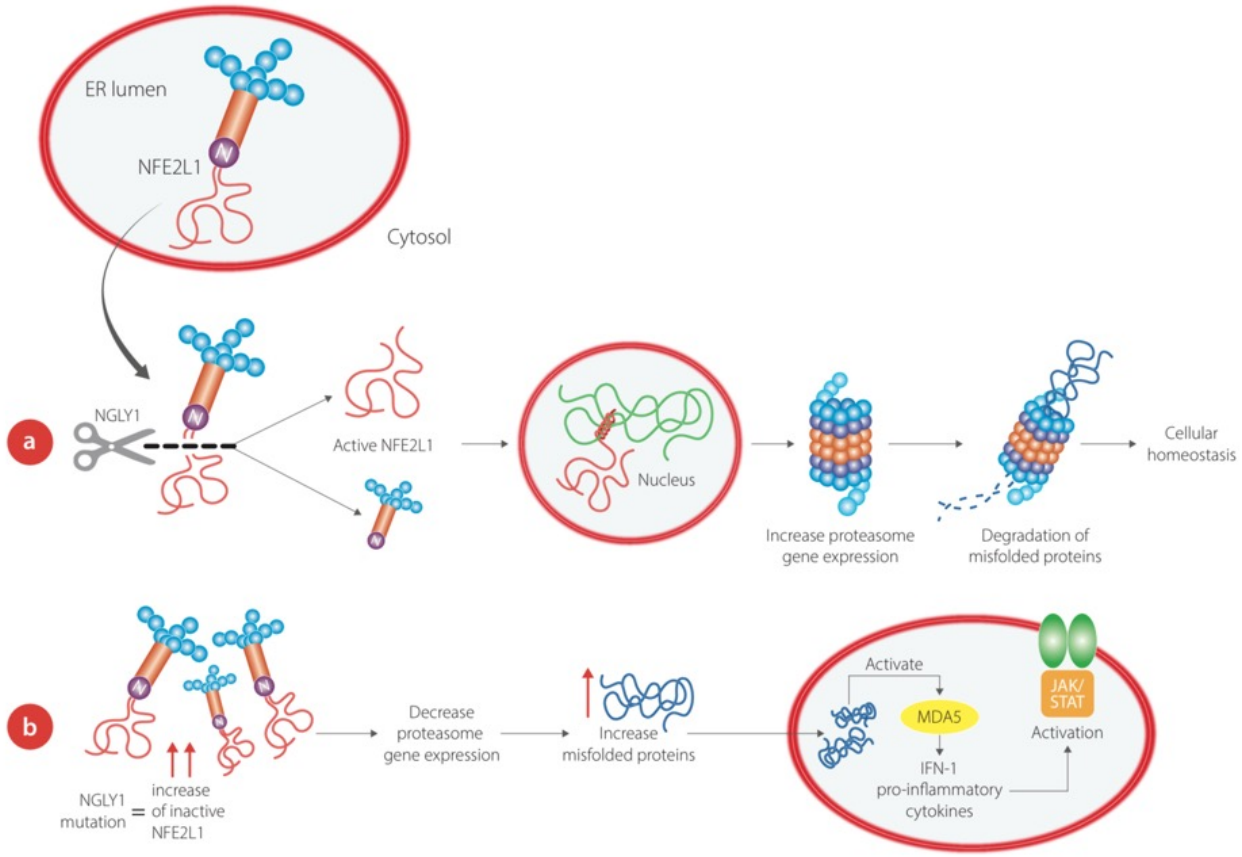


Figure 3. Proposed mechanism linking NGLY1 dysfunction to neuroinflammation. In the normal state A) misfolded glycoproteins within the endoplasmic reticulum (ER) are processed by NGLY1 which removes N-linked glycans and activates the transcription factor nuclear factor erythroid 2 related factor 1 (NFE2L1). Active NFE2L1 translocates to the nucleus and induces proteasome gene expression, promoting degradation of misfolded proteins and preservation of cellular homeostasis. In the presence of B) a pathogenic NGLY1 variant, defective deglycosylation leads to accumulation of inactive NFE2L1 and reduced proteasome activity, resulting in protein aggregation and cellular stress. Misfolded proteins may activate intracellular sensors such as melanoma differentiation-associated protein 5 (MDA5), which stimulates the Janus kinase/ signal transducer and activator of transcription (JAK/STAT) signalling cascade and upregulates type I interferons and pro-inflammatory cytokines. This pathway may contribute to neuroinflammation and dopaminergic neuronal dysfunction implicated in PD.

disruption and neuroinflammation[3–5].

In this patient, APS-3 and seronegative arthritis reflected a chronic state of systemic immune dysregulation that may have amplified central inflammatory pathways. Systemic inflammation is known to exacerbate motor symptoms in PD and may influence disease progression by increasing the allostatic burden on dopaminergic circuits. The decision to initiate tofacitinib was supported by evidence implicating the JAK/STAT pathway in neuroinflammation and by the drug's ability to cross the blood–brain barrier and modulate interferon signalling[6–9].

After more than 10 months of treatment, the patient demonstrated sustained clinical benefit: her APS-3 and musculoskeletal manifestations remained in remission, while parkinsonian rigidity and gait improved. Although a direct causal relationship cannot be established, the temporal association between JAK inhibition and motor improvement suggests that reducing systemic inflammation may have secondary neurological effects. This case highlights the potential role of immune modulation in neurodegenerative disorders with inflammatory comorbidity. It also supports the hypothesis that heterozygous NGLY1 variants may act as disease modifiers influencing PD phenotype or treatment response. Nevertheless, these findings should be interpreted cautiously, as single-patient observations cannot confirm causality. Further investigation—through mechanistic studies and controlled clinical trials—is warranted to explore the role of JAK inhibition and other immunomodulatory strategies in PD and related disorders characterized by neuroimmune interaction[6–10].

In this patient with PD and APS-3 carrying a heterozygous NGLY1 variant, treatment with tofacitinib was associated with sustained improvement in both motor and musculoskeletal symptoms. This observation supports the concept that neuroinflammation may contribute to symptom expression in PD and that immune modulation could influence disease manifestations in selected cases. The coexistence of genetic susceptibility and systemic autoimmunity illustrates how NGLY1 variants might act as disease modifiers through disruption of proteostasis and immune homeostasis. Further research is warranted to clarify the mechanisms linking inflammation and neurodegeneration and to define the potential role of JAK inhibition as an adjunctive therapeutic approach in PD with immune-mediated features.

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