

Miglustat Therapy for *SCARB2*-Associated Action Myoclonus–Renal Failure Syndrome

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Abstract

Objective

We evaluated whether substrate reduction therapy with miglustat could alter the course of action myoclonus–renal failure syndrome (AMRF), a rare, progressive myoclonic epilepsy with early mortality caused by scavenger receptor class B member 2 (*SCARB2*) gene mutations.

Methods

We identified an AMRF patient with a biallelic combination of *SCARB2* mutations determined by whole exome sequencing. *SCARB2* encodes a protein that traffics β -glucocerebrosidase to the lysosomal membrane. Mutations lead to a complex pattern of glucosylceramide accumulation and neurologic symptoms including progressive action myoclonus, seizures, and ataxia. We then evaluated the effect of inhibiting glucosylceramide synthesis, as is used in Gaucher disease. The patient was treated for 3 years with miglustat after several years of steady worsening.

Results

Progression of myoclonus halted, dysphagia resolved, some skills were reacquired, and seizures remained well controlled.

Conclusions

The response suggests that neurologic symptoms of *SCARB2*-associated AMRF could be ameliorated, at least partly, by targeting glycosphingolipid metabolism with available medications.

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Glossary

AMRF = action myoclonus–renal failure syndrome; **FSGS** = focal segmental glomerulosclerosis; **GCS** = glucosylceramide synthase; **GL1** = glucocerebroside; **LIMP-2** = lysosomal integral membrane protein type 2; **PD** = Parkinson disease; **SCARB2** = scavenger receptor class B member 2 gene; **UPJ** = ureteropelvic junction.

Action myoclonus–renal failure syndrome (AMRF) is a rare autosomal recessive progressive myoclonic epilepsy associated with renal disease and caused by scavenger receptor class B member 2 (*SCARB2*) gene mutations. Symptoms begin in the teens or twenties with tremor, myoclonus, ataxia, and epilepsy, characteristically sparing cognition.¹ Patients exhibit tremor in the fingers or hands exacerbated by activities such as handwriting, action myoclonus, bulbar myoclonus, and less prominent resting myoclonus of the face, trunk, and limbs. Seizures are often clonic-tonic-clonic. AMRF is relentlessly progressive with a 7- to 15-year lifespan from symptom onset.² *SCARB2* encodes lysosomal integral membrane protein type 2 (*LIMP-2*), a receptor for β -glucocerebrosidase (GCase, encoded by the glucosylceramidase beta gene, or *GBA*), which transports it from the endoplasmic reticulum to lysosomes, where the acidic environment activates its function. *SCARB2* mutations lead to impaired GCase trafficking and subsequent toxic accumulation of glucocerebroside (*GL1*) and its bioactive lipid, glucosylsphingosine.³

This glycosphingolipid pathway is also involved in Gaucher disease, in which *GBA* mutations lead to similar effects (Figure 1C). Substrate reduction therapy targeting *GL1* synthesis using glucosylceramide synthase (GCS) inhibitors are accepted therapies for Gaucher disease. The first-generation substrate reduction therapy, miglustat, is approved for mild type 1 Gaucher disease. Eliglustat is the most potent GCS inhibitor but does not cross the blood-brain barrier. Venglustat, a CNS-penetrant GCS inhibitor, is in trials for neuronopathic Gaucher disease and *GBA* mutation–associated Parkinson disease but was not available (compassionate use declined by the manufacturer). Miglustat exhibits modest CNS penetration and, in addition to Gaucher disease, is approved in Europe for treatment of Niemann-Pick disease type C. Hence, we assessed the response of AMRF to miglustat.

Methods

We conducted a trial in a patient with this rare, devastating disease that has no approved therapy. Whole exome sequencing was performed by array capture and high-throughput sequencing using an Illumina platform. The mean coverage of the exome was $>100\times$, and more than 98% of the exome had at least $20\times$ coverage. *SCARB2* variants in the proband were confirmed by Sanger sequencing. Targeted parental sequencing confirmed the inheritance pattern.

To confirm an effect on lysosomal function, leukocyte β -glucocerebrosidase activity was measured. We (P.K.M.) designed treatment with a GCS inhibitor (Figure 1C). Miglustat was started at 100 mg twice daily and increased to

200 mg 3 times a day over 6 months to improve brain delivery. This is the upper end of the dose range that has been used and tolerated in trials for Gaucher disease.⁴ Myoclonus was evaluated with video recordings and patient reports. Epilepsy, already well controlled via medications, was evaluated by patient seizure reporting and follow-up EEG.

Standard Protocol Approvals, Registrations, and Patient Consents

A waiver was obtained from the Yale University Human Investigation Committee (Institutional Review Board Registration #00011725). The patient provided informed consent for reporting her case.

Data Availability

Deidentified sequence data will be made available on reasonable request.

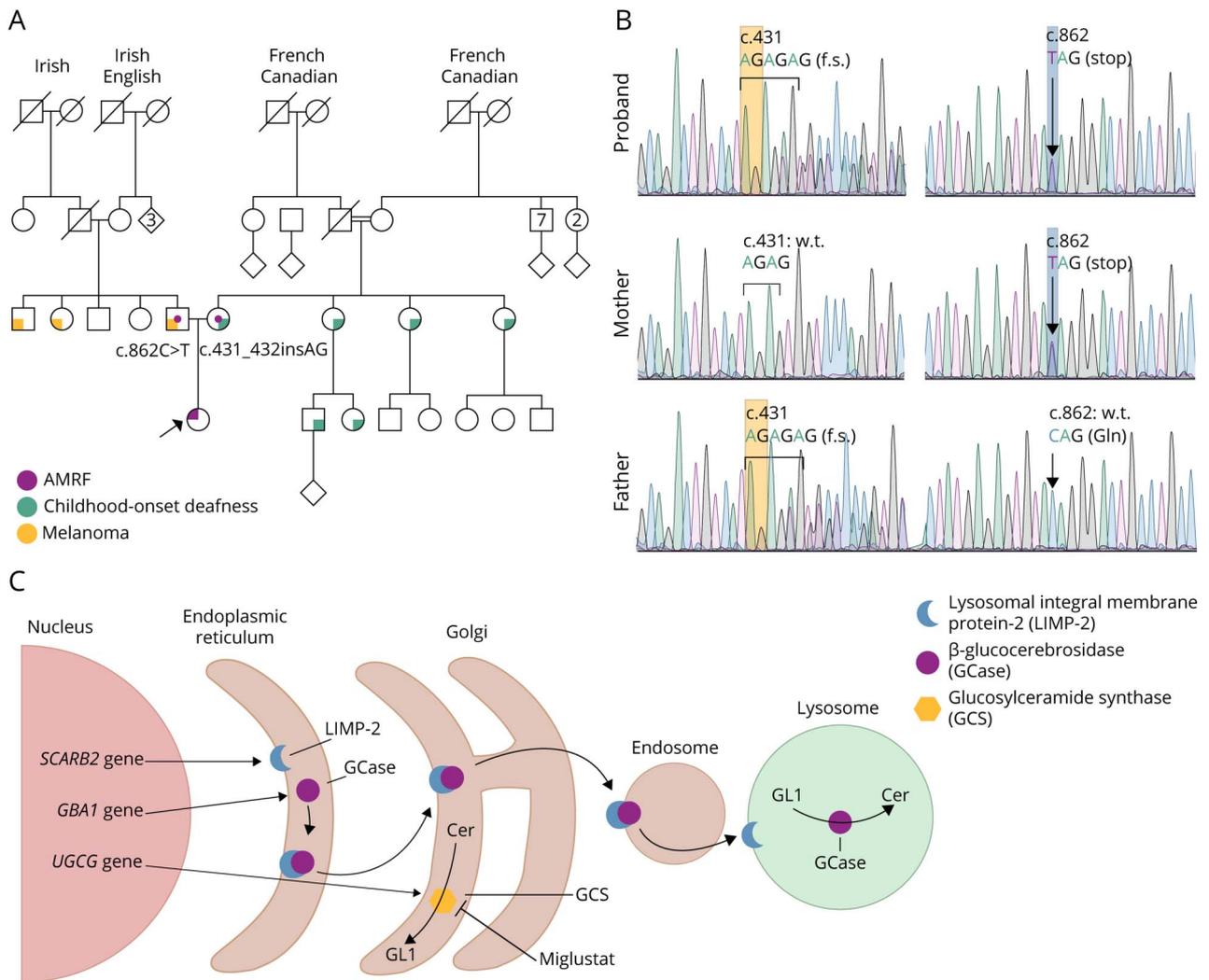
Results

The patient was a 25-year-old lawyer and dancer and presented with seizures and myoclonus. At age 20 years, she developed imbalance and falls with lower extremity jerking. At age 21 years, she developed upper extremity myoclonus and had the first of several bilateral tonic-clonic seizures. At age 22 years, her handwriting started to deteriorate. She developed dysarthria when fatigued. She required a cane at age 23 years and a walker at age 25 years because of lower extremity jerks. Concomitantly, she developed dysphagia. Family history included childhood-onset hearing loss on the maternal side and melanoma on the paternal side, but no seizures or movement disorders (Figure 1A).

Evaluation at age 25 years noted prominent bilateral action myoclonus in her upper more than lower extremities, titubation, wide-based gait, ocular dysmetria, and dysarthria. Mental status, strength, sensation, and reflexes were normal. A video EEG showed sleep-activated, low-amplitude, generalized polyspikes, a myoclonic seizure with a burst of central polyspikes, and innumerable myoclonic jerks without EEG correlates. Brain and spinal MRIs were unrevealing other than mild diffuse atrophy in 2019 compared with that in 2009. Clonazepam had no effect on myoclonus. L-dopa, levetiracetam, and perampanel had mild, transient effects. Valproate had a more sustained effect, but also mild. Clobazam was associated with worsening myoclonus. No medication had a sustained or dramatic response on myoclonus or any effect on progression of other symptoms (Figure 2).

After clinical genetic evaluation, whole exome sequencing revealed 2 pathogenic, biallelic, compound heterozygous

Figure 1 Patient With Action Myoclonus-Renal Failure Syndrome (AMRF) and Proposed Mechanism of Treatment



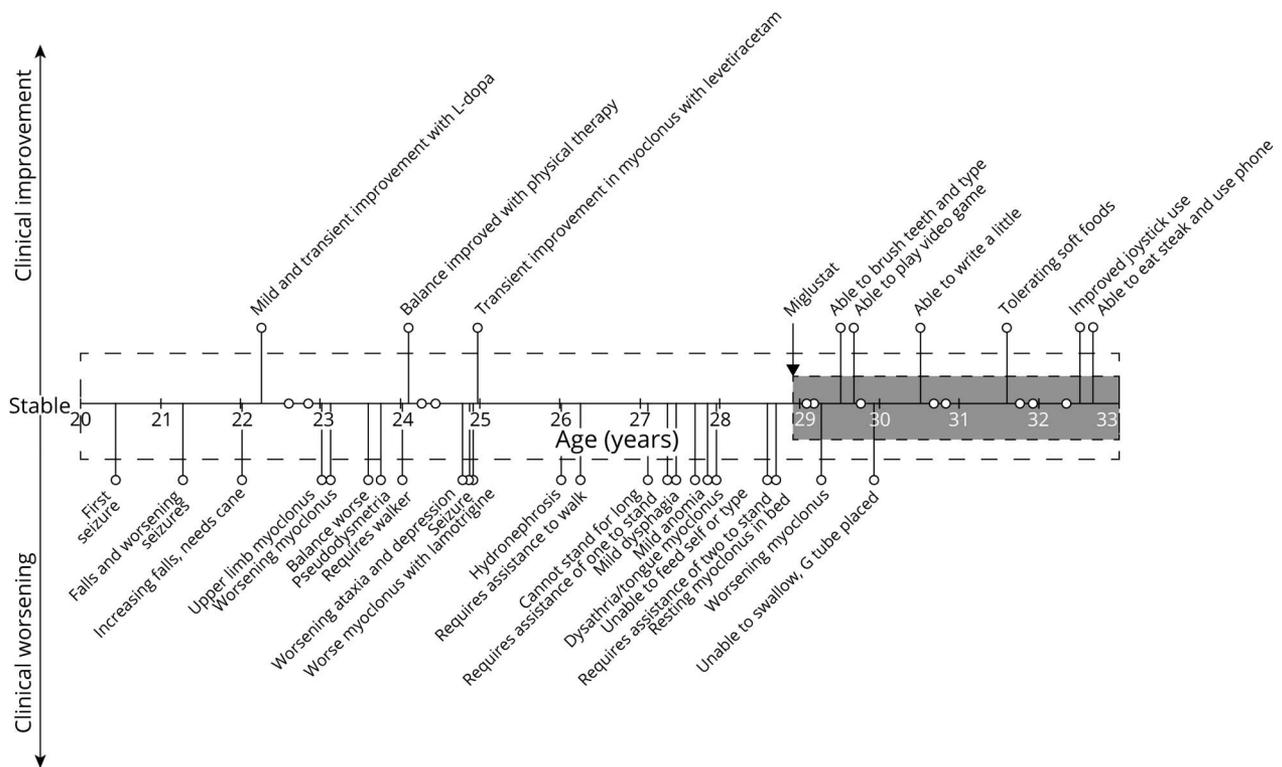
(A) Three-generational pedigree. There is no history of epilepsy or neurologic impairment in the extended family. The mother has isolated childhood-onset hearing loss, similar to her siblings and some of their offspring. The proband's maternal grandparents were first cousins. The father and his siblings have melanoma. The ancestry on the maternal side is French-Canadian and on the paternal side Irish-English. The parent's carrier status is indicated. (B) Sanger sequencing of DNA from the proband and parents showed that the proband inherited the 2 *SCARB2* variants independently (w.t. = wild type). A frameshift (f.s.) causing insertion at c.431 was inherited from the mother and is predicted to produce a premature stop codon and truncate the protein to 160 amino acids. A nonsense mutation at c.862 was inherited from the father and is predicted to either truncate the protein product at amino acid 288 or lead to nonsense-mediated mRNA decay of the transcript. (C) LIMP-2 binds β -glucocerebrosidase (GCCase, also called β -glucosidase, and encoded by *GBA1*) and transports it into lysosomes. GCCase normally catalyzes the conversion of lysosomal GL1 (also called glucosylceramide) to ceramide (Cer). Dysfunction of GCCase, whether from a *GBA1* mutation (Gaucher disease) or from impaired trafficking (*SCARB2* mutation, as in AMRF), causes GL1 accumulation. Miglustat antagonizes GL1 synthesis by inhibiting glucosylceramide synthase (also called ceramide glucosyltransferase and encoded by the uridine diphosphate-glucose ceramide glucosyltransferase gene or *UGCG*), preventing this toxic accumulation.

SCARB2 mutations (Figure 1B). One was an insertion of a dinucleotide repeat, c.431_432insAG on exon 4 (identical to c.435_436insAG), predicted to cause a frameshift and truncate the protein to 160 amino acids (full transcript encodes a 478 amino acid protein). The second, nonsense mutation c.862C > T (p.Gln288Ter) on exon 7 was predicted to cause loss of function through protein truncation or nonsense-mediated mRNA decay. Parental analysis confirmed that the mutations were independently inherited (Figure 1B). In homozygous cases, they were previously reported in unrelated individuals with AMRF.⁵ No pathogenic *GBA* variants were identified. Acid β -glucosidase activity in peripheral blood leukocytes was 7.5

nmol/h/mg protein, which, while lower than normal (≥ 8.7), was not in diagnostic range for Gaucher disease, where enzyme activity is typically less than 10% of normal value.

With miglustat dose escalation to 200 mg 3 times daily, multiple symptoms were ameliorated (Figure 2). Myoclonus and range of motion improved. The patient remained seizure-free. Dysphagia resolved completely; the patient was even able to eat pieces of steak again. EEG 18 months later showed no epileptiform discharges. Coordination and function improved modestly; for example, she was again able to use a joystick to play video games and to use the TV remote. There were no definite side effects.

Figure 2 Clinical Course



The disease progressed over the first few years from bilateral tonic clonic seizures and falls to worsening action myoclonus and gait to bulbar symptoms. After the initiation of miglustat, starting at 200 mg/d and titrated up to 600 mg/d, disease progression halted, and the patient regained skills, including the ability to type and use a mobile phone. Each clinic or hospital visit is marked with a circle, with vertical position indicating whether the patient reported new/worsening symptoms (low), improving symptoms (high), or no change (middle).

Although overall improvements were modest, the previously relentless neurologic progression stopped completely.

Renal function was normal with serum creatinine of 0.9 mg/dL at the time of genetic diagnosis. One year later, she developed right flank pain and hydronephrosis. Creatinine remained at 0.9 mg/dL, but proteinuria measured by spot urine testing was at 1.9 g/g creatinine. CT and retrograde pyelogram demonstrated a unilateral ureteropelvic junction (UPJ) obstruction from suspected congenital stricture. The obstruction was corrected with a stent, followed by pyeloplasty. Intraoperative renal biopsy (at age 26 years) showed early reflux nephropathy, but no evidence of glomerulosclerosis on light microscopy or podocyte effacement on electron microscopy. Over the next few years, she developed progressive renal insufficiency with creatinine rising to 1.42 mg/dL, but proteinuria declined to 0.23 g/g creatinine.

Discussion

We described a patient with AMRF due to biallelic *SCARB2* mutations with predicted loss of protein function. While these variants were previously identified in homozygous state in patients with AMRF,⁵ compound heterozygosity has not been described. The patient had prominent action myoclonus, controlled epilepsy, and dysphagia. Childhood-onset hearing

loss in the maternal family was suspected to represent a separate entity of hereditary nonsyndromic deafness. Because *SCARB2* mutations lead to GCase dysfunction and the patient was deteriorating rapidly, we assessed a trial of treatment with miglustat. Treatment resulted in arrest of progression of myoclonus, resolution of dysphagia, and mild overall sustained improvement over 3 years.

Treatment of AMRF with miglustat was described previously in 1 patient in 2011.⁶ In that report, 1 of the 2 siblings with AMRF (with homozygous *SCARB2* variants introducing premature stop codon p.Trp178Ter)⁷ was treated with miglustat 600 mg/d for 2 years starting at age 24 years, after earlier GCase enzyme replacement therapy with no improvement for 1 year. The patient's age at onset and presentation, apart from the renal features, were similar to the patient we have presented, including an EEG showing generalized discharges, antiseizure medications yielding only transient benefit, instability due to myoclonic jerks, and requirement for nasogastric tube. Similar to our patient, myoclonus improved and dysphagia resolved; however, that patient died of pneumonia at age 26 years.

Myoclonus and seizures in AMRF progress independently of renal failure.⁸ Usually, renal manifestations include proteinuria, which may be nephrotic, with histology revealing

interstitial fibrosis, atrophy, and focal segmental glomerulosclerosis (FSGS). However, some cases with certain biallelic *SCARB2* variants have been described as not having progressive renal failure from FSGS.⁹ In our patient, kidney biopsy showed no evidence of FSGS (not repeated since). Subsequently, creatinine has progressively but slowly increased without concomitant rise in proteinuria, as is more typical of progressive renal failure from FSGS, including cases of FSGS in AMRF. It is unknown whether the renal phenotype was slowed by the miglustat treatment or whether her AMRF represents a variant *SCARB2* mutation with milder kidney disease.

In addition, this patient had an anatomical UPJ obstruction, likely congenital, which was corrected surgically. She has not shown evidence of recurrent obstruction. However, the patient's kidney biopsy indicated fibrosis in a striped pattern, which can be seen in obstructive nephropathy. Thus, her slowly progressive loss of kidney function may be more consistent with chronic obstructive nephropathy. UPJ obstruction has not been reported in patients with AMRF,⁵ including the previously reported patient who was treated with miglustat and had different renal pathology than our patient.⁶ It is, however, seen in *Limp2*^{-/-} mice, which develop hydronephrosis due to UPJ obstruction and proteinuria with glomerular foot-process effacement, but not FSGS.¹⁰

The lysosomal pathway targeted in this case is important in other neurologic disorders. Human Parkinson disease (PD) brains have reduced GCase activity in substantia nigra.¹¹ *GBA* mutations are a risk factor of PD, and genome-wide association studies suggest that *SCARB2* variants may also increase PD risk.¹² Miglustat is a weak GCS inhibitor; a higher potency alternative with better brain penetrance, venglustat, is now in trials for *GBA* mutation-associated PD and neuronopathic Gaucher disease.^{13,14}

Although this is a single case, it provides confirmation to a prior case report of miglustat responsiveness from 10 years ago,⁶ and because AMRF is relentlessly progressive with no other available therapies, consideration should be given to miglustat or related medications in patients with mutations in *SCARB2* and conceivably other genes associated with impaired lysosomal metabolism. Our report is limited by subjectivity in reporting of myoclonus, dysphagia, and other symptoms. Future, larger, prospective trials should incorporate standardized scales for myoclonus and other symptoms. However, this therapy has the potential to be disease modifying, and we hope this report will encourage it to be tried early in the disease course as we gather additional evidence.

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Disclosure

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Anna M. Szekely, MD	Department of Neurology, Yale University School of Medicine, New Haven, CT	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
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Lawrence J. Hirsch, MD	Yale Comprehensive Epilepsy Center, Yale University School of Medicine; Department of Neurology, Yale University School of Medicine, New Haven, CT	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

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