Movement Disorders
CLINICAL PRACTICE
RESEARCH ARTICLE

Clinical Profile and Treatment Outcomes of Hypermanganesemia with Dystonia 1 and 2 among 27 Indian Children

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ABSTRACT: Background: Hypermanganesemia with dystonia 1 and 2 (HMNDYT1 and 2) are rare, inherited disorders of manganese transport.

Objectives: We aimed to describe clinical, laboratory features, and outcomes among children with HMNDYT.

Methods: We conducted a retrospective multicenter study involving tertiary centers across India. We enrolled children between 1 month to 18 years of age with genetically confirmed/clinically probable HMNDYT. Clinical, laboratory profile, genetic testing, treatment details, and outcomes scored by treating physicians on a Likert scale were recorded.

Results: We enrolled 27 children (19 girls). Fourteen harbored *SLC30A10* mutations; nine had *SLC39A14* mutations. The *SLC39A14* cohort had lower median age at onset (1.3 [interquartile range (IQR), 0.7–5.5] years) versus *SLC30A10* cohort (2.0 [IQR, 1.5–5.1] years). The most frequent neurological features were dystonia (100%; n = 27), gait abnormality (77.7%; n = 21), falls (66.7%; n = 18), and parkinsonism (59.3%; n = 16). Median serum manganese (Mn) levels among *SLC39A14* (44.9 [IQR, 27.3–147.7] mcg/L) cohort were higher than *SLC30A10* (29.4 [17.1–42.0] mcg/L); median hemoglobin was higher in *SLC30A10* (16.3 [IQR, 15.2–17.5] g/dL) versus *SLC39A14* cohort (12.5 [8.8–13.2] g/dL). Hepatic involvement and polycythaemia were observed exclusively in *SLC30A10* variants. A total of 26/27 children underwent chelation with disodium calcium edetate. Nine demonstrated some improvement, three stabilized, two had marked improvement, and one had normalization. Children with *SLC39A14* mutations had poorer response. Two children died and nine were lost to follow-up.

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Conclusions: We found female predominance. Children with *SLC39A14* mutations presented at younger age and responded less favorably to chelation compared to *SLC30A10* mutations. There is emerging need to better define management strategies, especially in low resource settings.

Hypermanganesemia with dystonia (HMNDYT) is a recently described neurogenetic disorder caused by abnormalities in intracellular manganese (Mn) transport.[1–4] Pathogenic variants in two Mn transporter genes have been reported. HMNDYT1 resulting from pathogenic variants in *SLC30A10* gene manifests typically with dystonia-parkinsonism, hepatic involvement, and polycythemia with depleted iron stores. Patients affected with *SLC39A14* mutations (HMNDYT2) develop rapidly progressive dystonia-parkinsonism with onset during early childhood, but lack hepatic involvement and polycythemia. In both conditions, pathognomonic magnetic resonance imaging (MRI) features include T1-weighted hyperintensities in basal ganglia, midbrain, dorsal pons, and medulla with characteristic sparing of the ventral pons.[2,3,5–8] Forty-five cases with *SLC30A10*[4,9–12] and 18 with *SLC39A14* mutations have been described.[4,13,14]

Treatment comprises chelation with disodium calcium edetate ($Na_2CaEDTA$) and iron supplementation. However, $Na_2CaEDTA$ is not widely available, incurs recurrent expenditure, monthly hospitalization and intravenous access, and therefore, presents several barriers in resource-constrained settings. Although treatment has been reported to be of benefit in case reports and case series, there is paucity of data on long term treatment outcomes.

In this multicentric retrospective study, we describe clinical, genetic, and radiological features and outcomes among Indian children with IH-Mn.

Methods

This was a retrospective, multicenter study across tertiary care hospitals in India with pediatric neurology expertise.

Participants

Children age 1 month to 18 years with genetically proven HMNDYT1/2 (ie, with mutations in *SLC30A10* or *SLC39A14* genes) diagnosed before March 1, 2019 were enrolled. We also included patients in who genetic analysis was not available, but the following features were present: extrapyramidal symptoms in the form of dystonia and/or parkinsonism; MRI brain showing T1 hyperintensities in basal ganglia; elevated blood/urine Mn levels; and absence of risk factors for acquired manganism like prolonged parenteral nutrition or environmental exposure. Children who had any other concurrent neurometabolic/neurodegenerative disorder or acquired neurological injury such as traumatic brain injury or meningoencephalitis were excluded.

Procedure

Details of clinical presentation, investigations, treatment regimen, and response were collected via a predesigned proforma. Clinical details included age at onset, presence of dystonia/parkinsonism, other movement disorders, cognitive impairment, seizures, vision, or hearing impairment.

MRI findings were reviewed by a neuroradiologist (K.M.). Because Mn is a paramagnetic element, magnetic susceptibility was expected on T1 and fluid attenuated inversion recovery (FLAIR) weighted sequences.[15,16] T1 shortening was graded on a qualitative scale as mild = 1+, moderate = 2+, strong = 3+.

Molecular genetic analysis was reviewed by two geneticists (U.S. and M.F.). A total of 23 patients had undergone next generation sequencing (NGS)/Sanger sequencing to identify underlying defects (additional data are listed in Table S1).

Treatment details included drugs used and duration of chelation, and supportive care for neurological and extra-neurological features. Treating clinicians rated treatment response in neurological features on a Likert scale (no change, somewhat improved, marked improvement, normalization, mild worsening, moderate worsening, and severe worsening). Results of available follow-up investigations such as liver function tests, hemogram, and serum/urinary Mn levels were noted.

Statistical Analysis

Data were recorded on an Excel spreadsheet and analyzed with SPSS version 22.0 (IBM group, Armonk, NY). Results were expressed as frequency (%), mean ± standard deviation or median (interquartile range).

Data Sharing

The data that support the findings of this study are available from the corresponding author on reasonable request.

Results

We enrolled 27 children with HMNDYT1/2 from 20 families (19 girls) (Tables 1 and 2). These included eight previously reported children.[5,9,17,18] Among these, 14 harbored *SLC30A10*

TABLE 1 *Detailed clinical and laboratory characteristics and treatment outcomes of individual patients with SLC30A10 mutations*

Subject no.	Subject	Sex	Age (y)	C	Onset age (y)	Dystonia	Other features	I	H	Hb (g/dL)	LFT	Mn (mcg/L)	Variant identified	Treatment outcomes
Children with SLC30A10 mutations														
1	F1[18]	F	8	+	5	+ (LL only)	Spasticity, brisk reflexes, recurrent falls	−	−	15.4	A	42.0	chr1:220101323G>A c.460C>T; p.Gln154*	Initial improvement on $Na_2CaEDTA$, but suboptimal. D-penicillamine added leading to further improvement. LFT normalized on treatment. She had severe polycythemia despite chelation and required four sessions of plasma exchange.
2	F2-C1[18]	F	9	+	2	+ (b/l feet)	Central hypotonia, chorea	−	+	15.6	A	23.9	chr1:220101291_220101291delG c.492delC; p.Gly165Alafs*27	Marked neurological improvement noted. LFT normalized. Hepatomegaly regressed.
3	F2-C2	F	2.5	+	2.0	+ (bilateral feet)	Choreiform and athetoid movements of hands and feet	−	−	17.5	A	29.2	chr1:220101291_220101291delG c.492delC; p.Gly165Alafs*27	Some neurological improvement. LFT normalized.
4	F2-C3[18]	F	7	+	2	+ (b/l toes)	−	−	−	11.4	N	29.5	chr1:220101291_220101291delG c.492delC; p.Gly165Alafs*27	Some neurological improvement although could not ambulate independently. LFT normalized.
5	F2-C4	F	2	+	1.5	+ (b/l feet and hands)	−	−	−	15.6	N	34.0	chr1:220101291_220101291delG c.492delC; p.Gly165Alafs*27	Patient showed initial improvement on $Na_2CaEDTA$, but suboptimal. D-penicillamine was added leading to further improvement from baseline. LFT normalized on treatment.
6	F2-C5	F	2.5	+	1.5	+ (b/l hands, feet)	Spasticity, brisk reflexes, tongue dyskinesia	−	−	15	N	42.0	chr1:220101291_220101291delG c.492delC; p.Gly165Alafs*27	Initial improvement on $Na_2CaEDTA$, but suboptimal. D-penicillamine was added leading to further improvement. LFT normalized on treatment.
7	F2[18]	M	4	+	3	+ (b/l LL)	Central hypotonia	−	−	16.3	A	19.5	chr1:220101291_220101291delG c.492delC; p.Gly165Alafs*27	Died in a road traffic accident.

(Continues)

TABLE 1 *Continued*

Subject no.	Subject	Sex	Age (y)	C	Onset age (y)	Dystonia	Other features	I	H	Hb (g/dL)	LFT	Mn (mcg/L)	Variant identified	Treatment outcomes
8	F3[9]	M	4.5	+	2	+ (b/l feet)	Parkinsonism	−	+	10.2 to >15.7	A	186.0	chr1:220101764_220101765insA; c.19_20insT (p.Lys7Ilefs*106	Initial improvement, then moderate worsening despite $Na_2CaEDTA$. Became non-ambulatory and developed progressive polycythemia.
9	F4	F	16	−	8	+ (b/l feet)	Spasticity, brisk reflexes	+	+	17.5	A	16.3	Chr1:220100449A>G; g.31541A>G; c.641-2A > G [Splice site]	Some neurological improvement noted. Hepatomegaly persistent.
10	F5	M	10.5	+	1.5	+ (all limbs)	Parkinsonism	−	−	17.0	N	10.0	chr1:220089243C>T; c.1006C>T; p.His336Tyr	Lost to follow-up.
11	F6	M	16	+	12	+	Bradykinesis, hypomimia, facial dystonia	+	−	16.6	A	UrineMn++	chr1:220089150C>T; c.1099C>T; p.Arg367*	Some improvement noted in gait, dystonia, cognitive functions.
12	F8[2]	F	5.5	+	5.1	+ (b/l feet)	Parkinsonism	−	+	21.4	A	130.0	chr1:220089203 T>C; c.1046 T>C;p.Leu349Pro	Some neurological improvement noted. Only three cycles of chelation given at the time of enrolment.
13	F9[18]	F	15	+	3	+ Gen.	Dysarthria, dysphagia	−	+	19.0	A	9.8	chr1:220101230_220101288del58 c.496_553del58 p.Ala166Glnfs*7	She received trihexyphenidyl, levodopa/carbidopa and oral iron supplementation. Because of unavailability, chelation therapy could not be offered. She required blood-letting twice.
Clinical exome sequencing negative														
14	F7	F	2.5	+	1.4	+ (b/l LL)	Spasticity, brisk reflexes	+	−	19.2	A	Serum and urine Mn++	No exonic pathogenic variations identified; UTR not covered	No improvement but no further deterioration noted. Partial exchange done for polycythemia.

Abbreviations: A, abnormal; AFO, ankle foot orthoses; ALT, alanine aminotransferase; AST, aspartate aminotransferase; b/l, bilateral; Br, bilirubin; C, consanguinity; F, female; Gen., generalized; H, hepatomegaly; I, incoordination; LFT, liver function test; LL, lower limb; M, male; Mn, manganese; N, normal; N/A, not available; S, sex; UL, upper limb.

TABLE 2 *Detailed clinical and laboratory characteristics and treatment outcomes of individual patients with SLC39A14 mutations and those with genetics unknown*

Subject no.	Subject	S	Age (y)	C	Onset age (y)	Dystonia	Other features	I	H	Hb (g/dL)	LFT	Serum Mn (mcg/L)	Variant identified	Treatment outcomes
Children with SLC39A14 mutations														
1	F10	M	5	+	3	+ Gen.	Parkinsonism, hyperreflexia	−	−	12.5	N	110.0	chr8:22265856A>G c.304A>G; p.Asn102Asp	Lost to follow-up.
2	F11	F	0.75	+	0.75	+ (trunk, b/l LL)	Intermittent opisthotonos	−	−	11.7	N	260.9	chr8:22262399 T>A c.176 T>A; p.Leu59Gln	No improvement, but no further deterioration noted.
3	F12	M	2	−	1.9	+ Gen.	−	−	−	12.8	N	60.5	Deletion of Exon4 to Exon9	Some improvement noted neurologically. Developed anemia on treatment.
4	F13[17]	F	1	−	0.75	+ Gen.	Brisk reflexes	−	−	12.5	N	200 (blood)	chr8:22265934C>T c.382C>T; p.Arg128Trp	Lost to follow-up.
5	F14	F	12	−	11	+ Gen.	Brisk reflexes, parkinsonism	+	−	11.7	N	28.5	chr8:22265874C>T c.322C>T; p.Arg108Trp	Lost to follow-up.
6	F14-C1	F	9	−	8	+ b/l LL	Brisk reflexes	−	−	11.4	N	29.3	chr8:22265874C>T c.322C>T; p.Arg108Trp	Lost to follow-up.
7	F15	F	2.75	−	0.33	+ LL>UL	Brisk reflexes, parkinsonism	+	+	8.8	N	23.5	chr8:22275310G>C; c.1294G>C; p.Ala432Pro	Lost to follow-up.
8	F16	F	2.6	+	1.25	+ (b/l ankles)	Lower limb hyperreflexia	+	−	14.5	N	Not done	chr8:22275329A>G; c.1313A>G; p.Tyr438Cys	Some improvement noted: stands with support, unbuttons shirt, tells stories, dry by night.
9	F17	F	1.2	+	0.67	+ Gen.	Brisk reflexes	−	−	8.8	N	↑ urine	chr8:22262404C>T c.181C>T; p.Gln61*	Some improvement noted.

(Continues)

TABLE 2 *Continued*

Subject no.	Subject	S	Age (y)	C	Onset age (y)	Dystonia	Other features	I	H	Hb (g/dL)	LFT	Serum Mn (mcg/L)	Variant identified	Treatment outcomes
Genetics not available														
1	F18	F	6	+	2	+ Gen.	Quadruped gait	−	−	10.1	N	20.8	N/A	Lost to follow-up.
2	F19	M	9.5	+	9	+ b/l UL	–	−	+	12.8	A	38.7	N/A	Died because of complications of liver disease.
3	F20	F	5.1	+	4	+ b/l feet	Parkinsonism, spasticity	−	−	12.5	A	72.9	N/A	Marked improvement: walks independently with AFO.
4	F21	M	2.75	+	1.5	+ (UL)	Central hypotonia, chorea-athetosis	−	+	9.8	A	↑ blood, urine	N/A	Lost to follow-up.

Abbreviations: AFO, ankle foot orthoses; ALT, alanine aminotransferase; AST, aspartate aminotransferase; b/l, bilateral; Br, bilirubin; C, consanguinity; F, female; Gen., generalized; H, hepatomegaly; I, incoordination; LFT, liver function test; LL, lower limb; M, male; Mn, manganese; N, normal; N/A, not available; S, sex; UL, upper limb.

mutations and nine had *SLC39A14* mutation (additional data are listed in Tables S1 and S2). Genetic confirmation could not be performed for four children, but all fulfilled clinical, radiological, and laboratory features of HMNDYT.

Median age at enrolment was 4.3 years (IQR, 2.5–9.0 years). Median age at onset for *SLC39A14* cohort was 1.3 years (IQR, 0.7–5.5 years), whereas for the *SLC30A10* cohort was 2.0 years (IQR, 1.5–5.1 years). Eighteen children were born to third-degree consanguineous and three to second-degree consanguineous parentage. The remaining six children had non-consanguineous parentage. Pedigree chart of the largest family affected is provided in Figure 1. Family history of dystonia was present in the largest family with HMNDYT1 (F2, F2-C1, F2-C2, F2-C3, F2-C4, and F2-C5). None of the other children had family history of dystonia.

Clinical Phenotype

The most frequent presenting complaint was gait abnormality (21/27; 77.7%) (Table 3). This varied from dystonic gait with toe-walking to the typical "cock-walk" gait. One patient developed a peculiar gait with partial walking on all fours, reminiscent of the gait in Uner Tan syndrome. Recurrent falls were common (18, 66.7%). Three children presented with abdominal complaints (jaundice/abdominal distention) preceding neurological complaints by 2 to 4 weeks. All three had *SLC30A10* mutations. Two children were non-ambulatory at presentation; both had *SLC39A14* mutations. Two children with *SLC30A10* mutations developed loss of ambulation during advanced stage (mean disease duration, 11 months); one while on chelation. Seizures were observed in two children (F16 and F20). In F16, who had HMNDYT2, onset of seizure was at 15 months of age, with sudden onset of up-rolling of eyes and loss of consciousness. This child developed three more similar episodes over the next 1.5 years. Electroencephalography (EEG) was normal. Levetiracetam was used for control of seizures. In F20, who was genetically uncharacterized, two episodes of generalized seizures occurred at 1.5 years of age, 2 weeks apart. EEG was normal. The child was initiated on valproate, which was eventually tapered and stopped after a seizure-free period of 2 years. Postural tremors involving both upper limbs, and chorea-athetosis were noted in five children each. Features of incoordination were present in four: dysdiadochokinesia (2), gaze evoked nystagmus (1), and gait ataxia (1). Eight had abnormal abdominal examination with clinically appreciable hepatic and/or splenic enlargement. Twelve children (44.4%) had spasticity involving limbs.

Laboratory Evaluation

Median blood Mn level among children with *SLC39A14* variants was 44.9 mcg/L (IQR, 27.3–147.7 mcg/L) and among those with *SLC30A10* variants was 29.4 (17.1–42.0 mcg/L) (Table 3). Among patients with *SLC30A10* variants, 13 of 14 (92.3%) children had polycythemia. Of 14 who had abnormal liver function test (LFT), 10 belonged to the *SLC30A10* cohort

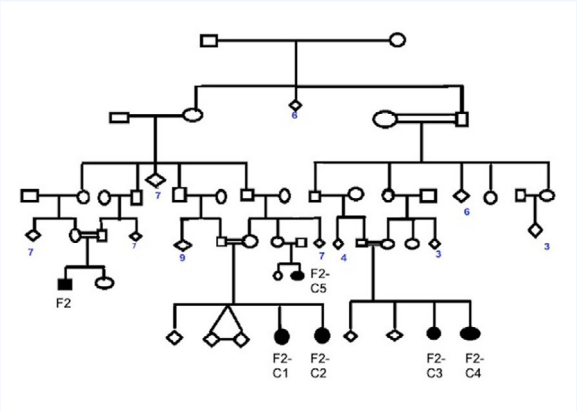

FIG 1. Pedigree chart of the largest family affected in our cohort.

and the other four had not undergone genetic testing, although presence of liver dysfunction in three indicated likelihood of underlying *SLC30A10* mutations. Thyroid function, tested in 18 children, was normal in all.

Genetic Abnormalities

Genetic analysis identified eight probands with *SLC30A10* variants and eight probands with *SLC39A14* variants. Importantly, no variant could be identified either in *SLC30A10* nor *SLC39A14* for one proband (F7) despite characteristic HMNDYT1 phenotype. Moreover, all genetic variants identified in either *SLC30A10* or *SLC39A14* genes existed in homozygous state. None of the patients carried compound heterozygous mutations. These variants were mostly not reported in gnomAD and 1KGP (1000 genome project) demonstrating their absence in the general population, except one variant in *SLC30A10* reported in ExAC in heterozygous state.

Mutations in *SLC30A10* included missense variants along with small indels in three cases (F2, F3, and F9) (additional data are listed in Tables S1 and S2). Of eight mutations, three were novel variants, a frameshift (p. Lys7Ilefs⋆106 in F3), a splice site change (c.641-2A>G in F4), and a nonsense variation (p.Arg367⋆ in F6) reported as likely pathogenic variations through ACMG guidelines (VARSOME; https://varsome.com).[19]

Mutations observed in the *SLC39A14* gene in our patient cohort were mostly missense variants with only one patient (F12) harboring a major deletion encompassing several exons (Ex4–Ex9) (additional data are listed in Tables S1 and S2). All variants in *SLC39A14* were novel except one, which is a reported pathogenic variation (p.Arg128Trp).[17] Among the novel variants, a large deletion of Exon4-Exon9 (F12) is reported to be pathogenic, whereas a nonsense change p.Gln61⋆ (F17) and missense variants like p.Ala432Pro and p.Tyr438Cys (F15, F16), respectively, were likely pathogenic The remaining missense mutations, p.Asn102Asp, p.Leu59Gln, p.Arg108Trp were classified as variant of unknown significance (VUS) following the American College of Medical Genetics and Genomics (ACMG) guidelines (VARSOME; https://varsome.com).[19]

However, location of these VUS in *SLC39A14* gene was confined to important functional domains of the SLC39A14 protein. p.Arg108Trp (shared by F14 and F14-C1 subjects), p.Asn102Asp (F10) fell in the extracellular N terminal domain, whereas p.Leu59Gln (F11) in the transmembrane domain 1 of SLC39A14, similar mutations in these domains are known to alter function.[5] The p.Arg108Trp variation is predicted benign (DEOGEN2, EIGEN, FATHMM-MKL, MVP, MutationTaster, PrimateAI, and REVEL), and pathogenic (DANN, LIST-S2, M-CAP, MutationAssessor, and SIFT) within an evolutionary non-conserved site, whereas p.Leu59Gln has transmembrane domain location and predicted majorly as pathogenic by prediction tools, BayesDel_addAF, DANN, EIGEN, FATHMM-MKL, LIST-S2, M-CAP, MutationAssessor, MutationTaster, and SIFT. The functional consequence of nonsense mutations and indels revealed that the occurrence of a premature stop codon either results in formation of truncated protein or complete loss of functional protein because of nonsense mediated decay of the transcript. Missense variants in both *SLC30A10* (F5, F8) and *SLC39A14* (F10, F11, F13, F14, F15, and F16) were mostly present at transmembrane domains, involved in binding and trafficking of metal ions, therefore, likely hindering protein function.

Loss of functional genomic variants in either *SLC30A10* or *SLC39A14* did not result in higher Mn levels in all patients. Henceforth, a genotype–phenotype correlation could not be observed. However, Mn levels were found to be more elevated in patients carrying *SLC39A14* variants than *SLC30A10* carriers. In *SLC30A10*, only two cases showed substantial increase in Mn levels; p.Lys7⋆(F3), which is predicted to truncate almost the full length of the protein, and in case F8, a nonsynonymous p.Leu349Pro variant in regulatory cytoplasmic C-terminal domain (CTD). This domain has a role in structure and stability of SLC30A10 protein.

Radiology

Marked T1-shortening was demonstrated in all cases (additional data are listed in Table S3). Within the basal ganglia, globus pallidus was most strongly involved, followed by subthalamic nucleus, putamen, substantia nigra, and caudate nucleus. The thalamus was characteristically spared in majority. We also observed a generally increased T1-weighted white matter signal also in periventricular and deep white matter of the cerebral hemispheres, as well as within the cerebellar peduncles in the majority of cases. We also noted involvement of the dentate nuclei. Parenchymal atrophy was not noted.

Six patients underwent post-treatment MRI. We observed dramatic improvement in the extent of T1 shortening, with residual changes mostly in the globus pallidus, internal capsule and or subthalamic nucleus. In three cases, T2-weighted sequence showed central gliosis within the globus pallidus, especially on post treatment follow-up (Fig. 2).

Among children with *SLC30A10* mutations, 8/14 children demonstrated hepatomegaly on ultrasonography with or without

TABLE 3 *Clinical features and laboratory evaluation of patients with HMNDYT*

Clinical features	Total (n = 27)	*SLC30A10* mutations (n = 14)	*SLC39A14* mutations (n = 9)
Median age (y) (IQR)	4.3 (2.5–9.0)	5.5 (2.7–9.8)	2.3 (1.0–6.4)
Sex			
Female (%)	19 (70.4)	10 (71.4)	7 (77.8)
Median age at onset (y) (IQR)	2.0 (1.5–5.0)	2.0 (1.5–5.1)	1.3 (0.7–5.5)
Prominent complaints			
Gait abnormality/Falls	21/18	12/14	4/–
Dystonia	27	14	9
Regression of milestones	3	1	2
Dysarthria	3	2	–
Abdominal[a]	3	2[a]	–
Seizures	2	–	1
Tremors	5	2	1
Non-ambulatory at presentation	2	–	2
Consanguinity			
Second degree/third degree	3/18	1/11	–/5
Examination findings			
Cognitive dysfunction	3	1	1
Motor system			
Spasticity	12	5	7
Extrapyramidal system			
Dystonia (generalized)	27 (21)	13 (12)	10 (8)
Tremor	5	2	1
Parkinsonism	16	11	4
"Cock-walk" gait	8	6	2
Chorea-athetosis	5	2	2
Dysarthria	8	6	2
Incoordination	4	2	2
Abdominal examination			
Hepatomegaly/Splenomegaly	8	4	1
Laboratory parameter			
Hb (g/dL)			
Mean	12.8	16.1	11.7
SD	3.3	2.9	2.3
Median	13.8	16.3	12.5
IQR	11.4–16.4	15.2–17.5	8.8–13.2
PCV			
Mean	42.1	48.5	36.2
SD	9.5	8.4	6.3

(Continues)

TABLE 3 *Continued*

Clinical features	Total (n = 27)	*SLC30A10* mutations (n = 14)	*SLC39A14* mutations (n = 9)
Median	40.8	49.5	37.5
IQR	35.5–49.9	46.1–55.6	29.5–41.7
Liver function test (LFT)			
Normal	13	3	9
Abnormal	14	11	–
Hyperbilirubinemia	6	6 (all mild)	–
Elevated SGOT	8	6	–
Elevated SGPT	5	6	–
Elevated ALP	5	5	–
Hypoalbuminemia	4	3	–
Abdominal imaging[b]			
Normal	15	6	9
Hepatomegaly with increased echotexture	3	2	–
Hepatomegaly with normal echotexture	5	5	–
Splenomegaly	1	–	–
Others[c]	1		
Serum manganese level (0.3–1.8 mcg/L)	n = 21	n = 12	n = 6
Mean	58.1	47.7	85.4
SD	63.9	53.9	91.9
Median	32.5	29.4	44.9
IQR	22.2–66.7	17.1–42.0	27.3–147.7
Thyroid function test (n = 18)	Normal		

[a]In one child, the abdominal complaint (jaundice) accompanied the neurological complaints. In the second child, abdominal complaints preceded neurological complaints be 2 weeks and in the third by 4 weeks.
[b]Ultrasonography abdomen: 22; MRI abdomen = 1; CT abdomen = 1.
[c]Splitting of the pelvi-calyceal system noted.
Abbreviations: IQR, interquartile range; PCV, packed cell volume; SD, standard deviation; SGOT, serum glutamic oxaloacetate transaminase; SGPT, serum glutamic pyruvic transaminase.

increased liver echotexture. Interestingly, hepatomegaly with normal liver echotexture was also reported in one child with *SLC39A14* mutations. All these children also had clinically appreciable liver enlargement. MRI abdomen, done in one patient with *SLC30A10* mutations, showed increased T1 and low T2 signal in the liver.

Treatment Outcomes

Among the 27 children, 26 were treated with $Na_2CaEDTA$ (regimen: 20 mg/kg per dose, given twice daily, for 5 days. Solution prepared in 250 mL 0.9% sodium chloride, and administered over 1 hour). In addition, iron was supplemented orally in 22 and oral zinc in 16 children. D-penicillamine was used in two children. Several drugs for symptomatic treatment including trihexyphenidyl, clonazepam, levodopa/carbidopa, baclofen, and botulinum toxin were also used.

In our series, 16 children continued to be on regular follow-up, for a median duration of 2.0 (IQR, 0.7–3.0) years; nine were lost to follow-up (Table 4). Two children died, one because of complications of chronic liver disease and one in a road traffic accident. Neurological outcomes on treatment were scored by treating physicians on a Likert scale. Nine of 16 children had some improvement and three had stabilization with no further deterioration (additional data are listed in Table S4 and Video 1). Only two children had marked improvement, and one had normalization. One child had moderate worsening after some initial improvement. Among nine children with some improvement, two had suboptimal improvement on chelation with $Na_2CaEDTA$ and were placed on additive d-penicillamine, following which they showed some improvement. On

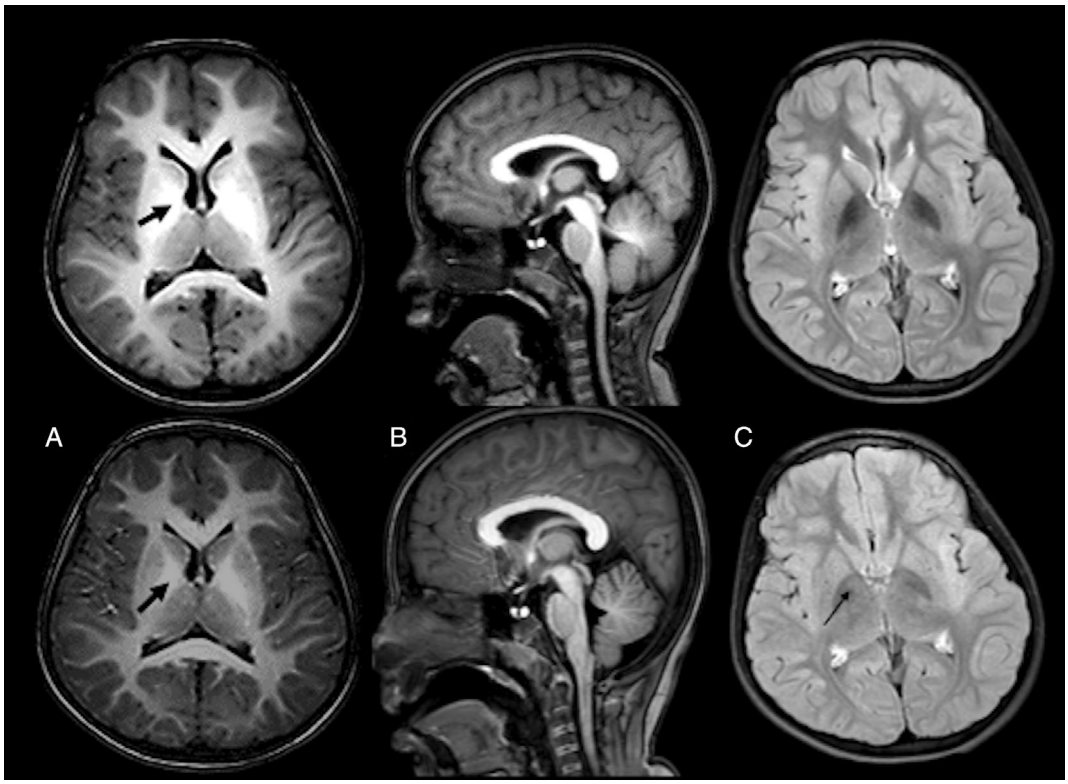

FIG 2. Case F20. Top panel (a = axial T1, B = sagittal T1, C = FLAIR) shows presentation scans. Bottom panel shows corresponding post treatment images. Note the reduction in swelling and T1 shortening globally within the white matter, particularly within the globus pallidi (arrows) and the tegmentum and superior cerebellar peduncles. The axial FLAIR images show concomitant reduction in the hypointensity within the globus pallidi, but with some increased central focal hyperintensity (C-arrow), which would be consistent with mild central pallidal gliosis.

comparing children with some to marked improvement (n = 12) versus no improvement to worsening (n = 4) (Table S4), it was observed that the latter group had later median age at presentation and shorter duration of chelation compared to children with improvement. Of four children with *SLC39A14* variants with available follow-up, one stabilized and three showed some improvement.

Of 15 children with abnormal liver function tests, follow-up reports were available for 10 children; among these, hepatic parameters normalized for seven and remained stable for three children without further progression. Among eight children with hepatomegaly, one showed regression in liver size with treatment. Hepatomegaly stabilized among the remaining six children. Three children continued to have worsening polycythemia despite chelation (F1, F3, and F8) of whom one child required partial exchange for hyperviscosity syndrome (F1) (Table 1). One child (F9) required phlebotomy twice for hyperviscosity, but she had been off chelation because of non-availability of $Na_2CaEDTA$ at the time. None of these children had clinical features of hyperviscosity and a hematocrit cut-off of 70% and above prompted phlebotomy.

Follow-up urinary and serum Mn levels could be measured in only four children who demonstrated increase in urinary Mn excretion during chelation therapy: F1, 99.3 to 699 mcg/L, serum 42 to 17.8 mcg/L; F2, 8.33 to 253 mcg/L, serum 19.5 to 11.2 mcg/L; F2-C1, 3.43 to 81.5 mcg/L, serum 23.9 to 16.2 mcg/L; F2-C3, 5.66 to 285 mcg/L, serum 29.5 to 18.2 mcg/L. Repeat serum manganese levels persisted to be high despite 12 to 18 months of chelation therapy.

Discussion

To the best of our knowledge, this is the largest case series of children with HMNDYT. Patients with *SLC39A14* mutations were younger at symptom onset (50% had onset in infancy) and at presentation, compared to patients with *SLC30A10* mutations. This is consistent with original descriptions of *SLC39A14* mutations-related HMNDYT among 10 children with mean age at onset being 15.8 (7–36) months compared to *SLC30A10* with mean age at onset of 7.1 (1–57) years.[6] We also noted a strong female predominance, with female:male ratio being 2.25:1. Although female preponderance has been noted in previous reports, we found a higher female proportion than previously observed.[6]

TABLE 4 *Treatment outcomes among children with HMNDYT*

	Total	*SLC30A10* mutations	*SLC39A14* mutations
Patients continuing to be on follow-up	16	11	4
Lost to follow-up	9	2	5
Died[a]	2	1	–
Duration of follow-up available (yrs)	n = 16		
Median	2.0		
IQR	0.7–3.0		
Neurological course on treatment			
Stabilized[b]	3	2	1
Some improvement[b]	9	6	3
Marked improvement	2	1	–
Normalization	1	1	–
Mild worsening	–	–	–
Moderate worsening[c]	1	1	–
Severe worsening	–	–	–

[a]Died in a road traffic accident = 1; died because of liver dysfunction = 1.
[b]In 3 patients, because of suboptimal response with $Na_2CaEDTA$, d-penicillamine was added leading to some improvement from baseline in two and stabilization of the disease in one patient.
[c]The patient showed initial improvement followed by moderate worsening.

Video 1. Pre-chelation (segment A) (at age 4 years) and post-chelation (segment B) (at age 9 years) videos of a child with *SLC3010* mutation (F2-C1), demonstrating abdominal distention (hepatomegaly) and dystonic gait pre-chelation. The same child demonstrates regression of abdominal distention and improvement of lower limb dystonia after 4 years of chelation therapy.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13516

Neurological presentation was dominated by extrapyramidal features including dystonia, parkinsonism, chorea-athetosis, and tremors, although we also found mild cerebellar features in some children. The most common presenting complaint was gait abnormality, which ranged from dystonic gait with toe-walking to the typical "cock-walk" gait.

We evaluated phenotypic association of each of the reported and identified novel variants. Overall, locations of each of the missense variants in both *SLC30A10* (F5, F8) and *SLC39A14* (F10, F11, F13, F14, F15, and F16) were confined to functional domains like transmembrane domains, involved in binding and trafficking of metal ions, and hence, may hinder protein function and lead to pathogenic effects. Missense protein truncating variants were identified as well. There was lack of overall understanding of genotype–phenotype correlation for each of the variants; however, some of the observations are described for *SLC30A10* and *SLC39A14* overall.

Children with *SLC39A14* variants seemed to have more severe neurological disease. Most had generalized dystonia, with two being non-ambulatory and one requiring support to walk at presentation. In contrast, most children with *SLC30A10* mutations had lower limb (foot/toe) dystonia, but were independently ambulatory despite recurrent falls until advanced stage.

Liver dysfunction and hepatomegaly were observed exclusively among children with *SLC30A10* mutations. The lack of hepatic Mn deposition in *SLC39A14* mutations has been partly attributed to impaired hepatic Mn uptake, believed to be a function of the SLC39A14 protein.[5] In knockout (KO) mouse models with deficient *SLC30A10* and *SLC39A14* transporters individually as well as together (double KOs), elevated Mn levels could be demonstrated in all three models in blood and brain, but increased hepatic Mn was demonstrable only in the *SLC30A10* model.[20,21] Another

interesting observation in our study was that with chelation, LFTs normalized in several patients, suggesting reversibility in early stages.

Presence of polycythemia was seen exclusively with *SLC30A10* mutations, in line with previous reports, with some children demonstrating severe polycythemia. However, the proportion of polycythemic children is much higher in our series than noted previously.[6] This is interesting, considering that children in our resource-constrained settings often exhibit anemia, and hence, normal Hb values usually raise concerns of relative polycythemia. Mn may mimic effects of hypoxia, stabilize hypoxia-inducible factor (HIF), and induce genetic expression of erythropoietin (Epo) leading to increase in Hb,[22,23] supported by raised Epo levels in some patients. Elevated Mn levels activate HIF-1 and 2, to upregulate SLC30A10, which reduces cellular Mn levels. This mechanism and subsequent polycythaemia may be absent in HMNDYT2 because of lack of hepatic involvement.[24]

Apart from brain and liver, thyroid dysfunction, presumably because of accumulation of Mn in thyroid tissue, has been demonstrated in *SLC30A10* KO mice,[21,25] with severe hypothyroidism because of inhibition of thyroxine hormone by Mn. However, we did not observe any thyroid dysfunction.

Neuroimaging is useful not only for diagnosis, but also to monitor therapeutic response. We found classic T1 shortening of basal ganglia in all children. Post-chelation scans demonstrated dramatic improvement in the extent of T1 shortening, with residual changes mostly in the globus pallidus, internal capsule, and/or subthalamic nucleus. This is in line with the few case reports where repeat imaging has been described.[8,26,27] Hence, MRI scans can be used to monitor treatment response. However, limitations of cost and need for sedation in young children need consideration. Optimal timing for follow-up scans needs to be determined as well.

Treatment outcomes on chelation with $Na_2CaEDTA$ among our patients were variable. Although most patients on follow-up had some alleviation of neurological symptoms, marked improvement/ normalization was achieved in very few. Children with deterioration had shorter duration of chelation and presented somewhat later than children who showed improvement, which may be important influencers of outcome. However, these results must be interpreted with caution owing to small patient numbers, and predictors of outcome require careful evaluation in larger cohorts. Long-term treatment outcomes on chelation have been reported in a few patients. A 10-year follow-up of a patient with *SLC30A10* variant observed good clinical and biochemical response with chelation therapy with $Na_2CaEDTA$, but reduction in MRI T1 signal change occurred only after 4 years.[8] The patient showed clinical deterioration when d-penicillamine was substituted, because of lack of availability of $Na_2CaEDTA$. In another adult patient with *SLC30A10* variant, a 2-year follow-up revealed significant improvement in parkinsonism and hepatic steatosis.[28]

We also noted a large proportion of loss to follow-up, particularly in children with *SLC39A14* mutations. This may be because of suboptimal response after the first few cycles of chelation, as well as recurrent need for hospitalization. Apart from limited availability of $Na_2CaEDTA$ in India, its use necessitates hospitalization and monthly intravenous infusion for 5 days. This demanding regime leads to parental fatigue, loss of work, and school days and consequent loss to follow-up. Additionally, potential side effects of chelation therapy include hypocalcemia (that may develop during infusion), trace metal and vitamin deficiency, low platelets and leucopenia, and nephrotoxicity. Therefore, related monitoring needs to be done regularly, including renal function, complete blood count, calcium/phosphate, and trace metal (copper, zinc).

Previously, the use of oral 2,3-dimercaptosuccininc acid as well as d-penicillamine has been trialed in some patients with varying benefits.[7,8,26,27,29] D-penicillamine as an add-on agent in two of our patients yielded appreciable results. D-penicillamine may serve as a more feasible agent in our settings, because it is orally administered, widely available, and inexpensive.

Limitations of our study include its retrospective nature and loss to follow-up of a large proportion of patients. Repeat serum/urinary manganese levels and neuroimaging were not available in most children. These tests are very expensive and not easily available in India. There are no guidelines for using serum/urinary manganese levels to titrate chelation. Furthermore, we could not apply functional scales to assess baseline and post-treatment disease severity and used a Likert scale instead. It will be useful to design severity scales and functional scoring in future studies.

Conclusions

We report clinical presentation and short term outcomes of children with HMNDYT in a low-resource setting. We found female preponderance in both genetic subtypes, younger age at onset and more severe clinical phenotype in children with *SLC39A14* mutations, and moderate response to $Na_2CaEDTA$ chelation therapy overall. Our study raises concerns regarding treatment options in these patients, inviting the possibility of exploring further therapeutic options such as d-penicillamine in the future.

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Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

D.G.: 1A, 1B, 1C; 2A, 2B, 2C; 3A, 3B

S.Y.: 1A, 1B, 2C, 3C

M.F.: 1A, 1B, 2C, 3C

U.S.: 1A, 1B, 2C, 3C
K.M.: 1A, 1B, 2C, 3C
P.G.: 1A, 1B, 2C, 3C
V.B.: 1A, 1B, 2C, 3C
A.B.: 1A, 1B, 2C, 3C
U.K.: 1A, 1B, 2C, 3C
A.G.S.: 1A, 1B, 2C, 3C
N.S.: 1A, 1B, 2C, 3C
K.S.: 1A, 1B, 2C, 3C
V.K.G.: 1A, 1B, 2C, 3C
M.J.: 1A, 1B, 2C, 3C
M.K.: 1A, 1B, 2C, 3C
H.P.: 1A, 1B, 2C, 3C
D.P.: 1A, 1B, 2C, 3C
S. Pa.: 1A, 1B, 2C, 3C
V.U.: 1A, 1B, 2C, 3C
A.K.: 1A, 1B, 2C, 3C
S.P.: 1A, 1B, 2C, 3C
M.T.: 1A, 1B, 2C, 3C
S.D.: 1A, 1B, 2C, 3C
A.Sh.: 1A, 1B, 2C, 3C
A.S.: 1A, 1B, 2C, 3C
H.P: 1A, 1B, 2C, 3C
V.S: 1A, 1B, 2C, 3C
S.S.: 1A, 1B, 1C; 2A, 2B, 2C; 3B, 3C.

Disclosures

Ethical Compliance Statement: Ethical clearance for this study was obtained from the Ethics Committee for Human Research of Lady Hardinge Medical College (Reference LHMC/IEC/2019/31R) and other participating institutes as necessary by their local ethics committees. Informed consent was obtained from the participating parents, and assent from the child when applicable. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

Table S1. Variants identified in patients with associated genetic and clinical interpretation.

Table S2. Methodology deployed for genetic screening.

Table S3. MRI features among children with inherited hypermanganesemia.

Table S4. Differences between children with no improvement/worsening versus some/marked improvement (n = 16).