BRIEF REPORT

Brain Dopamine–Serotonin Vesicular Transport Disease and Its Treatment

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SUMMARY

We describe a disease encompassing infantile-onset movement disorder (including severe parkinsonism and nonambulation), mood disturbance, autonomic instability, and developmental delay, and we describe evidence supporting its causation by a mutation in *SLC18A2* (which encodes vesicular monoamine transporter 2 [VMAT2]). VMAT2 translocates dopamine and serotonin into synaptic vesicles and is essential for motor control, stable mood, and autonomic function. Treatment with levodopa was associated with worsening, whereas treatment with direct dopamine agonists was followed by immediate ambulation, near-complete correction of the movement disorder, and resumption of development.

Known disorders of biogenic amine neuromediators (dopamine, norepinephrine, epinephrine, and serotonin) involve defects in nine enzymes[1-9] and one transporter.[10] Affected persons present in early childhood with symptoms referable to the affected neurotransmitter, and the disorders are diagnosed by measurement of neurotransmitter breakdown products in the cerebrospinal fluid (CSF). A deficiency in dopamine results in movement disorder; deficient norepinephrine or epinephrine causes autonomic dysfunction; and serotonin deficiency leads to sleep and psychiatric disturbances.[2,3,6]

We describe members of a family with symptoms of deficiencies in dopamine (dystonia, parkinsonism, and oculogyric crises), serotonin (sleep and mood disturbance), and epinephrine and norepinephrine (diaphoresis, temperature instability, ptosis, and postural hypotension), with no demonstrable deficiency of neurotransmitters in the CSF. Genome investigation revealed a mutation in the gene encoding VMAT2 that compromises transport of biogenic amines into synaptic vesicles, resulting in impairment of their synaptic transmission without detectable reductions in their amounts.

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CASE REPORT

Eight children of an extended consanguineous Saudi Arabian family had similar clinical symptoms of a complex movement disorder that was inherited in an autosomal recessive fashion (Fig. 1A; and Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The parents were unaffected, but at least five had clinical depression.

The index patient, when she presented to us, was a 16-year-old girl with global developmental delay and abnormal movements. She had first been brought to medical attention at 4 months of age with hypotonia, loss of acquired head control, and paroxysmal stereotyped episodes of persistent eye deviation and crying

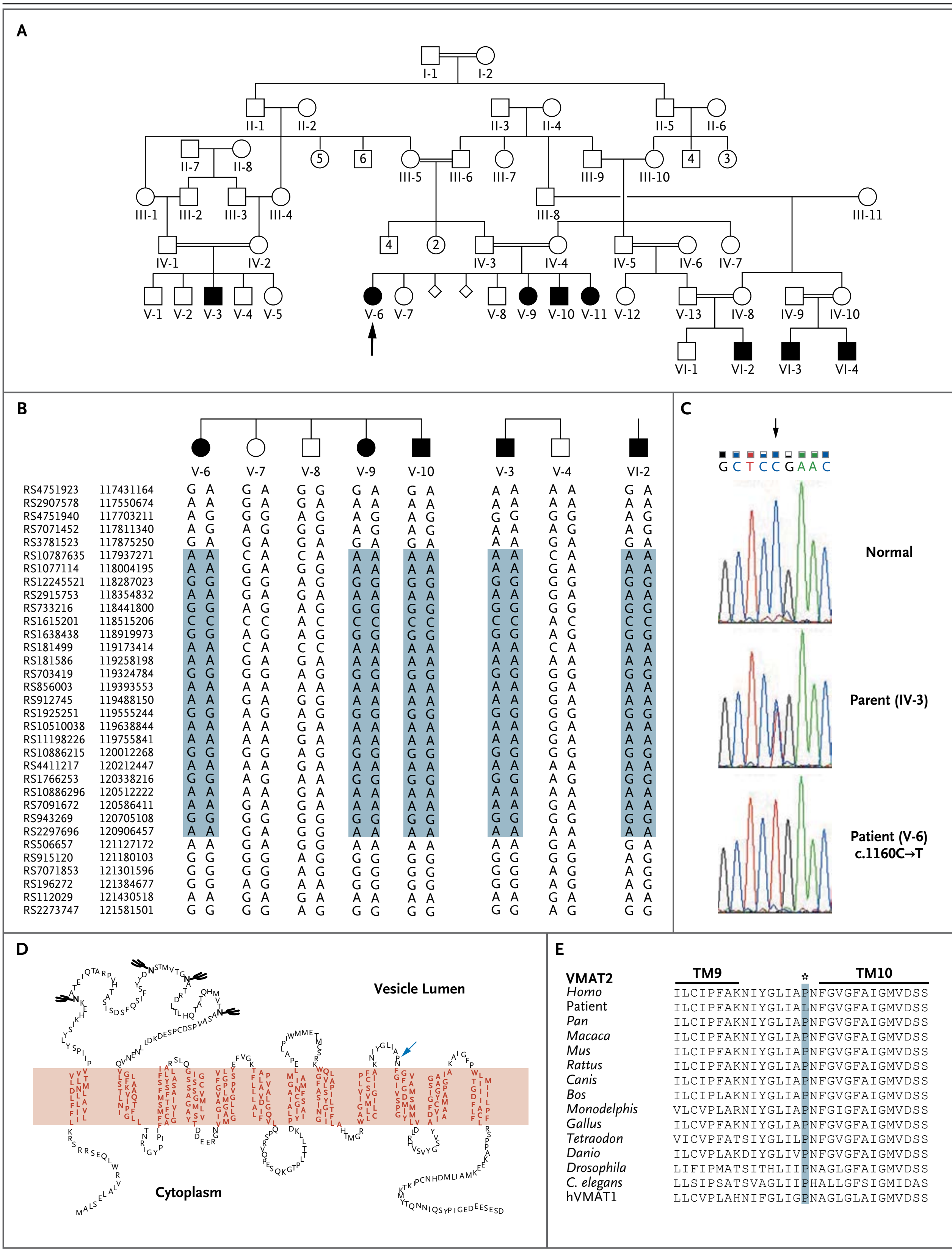
A
B
C
Normal
Parent (IV-3)
Patient (V-6)
c.1160C→T
D
Vesicle Lumen
Cytoplasm
E
VMAT2
TM9
TM10
Homo ILCIPFAKNIYGLIAPNFGVGFAIGMVDSS
Patient ILCIPFAKNIYGLIALNFGVGFAIGMVDSS
Pan ILCIPFAKNIYGLIAPNFGVGFAIGMVDSS
Macaca ILCIPFAKNIYGLIAPNFGVGFAIGMVDSS
Mus ILCIPFAKNIYGLIAPNFGVGFAIGMVDSS
Rattus ILCIPFAKNIYGLIAPNFGVGFAIGMVDSS
Canis ILCIPFAKNIYGLIAPNFGVGFAIGMVDSS
Bos ILCIPLAKNIYGLIAPNFGVGFAIGMVDSS
Monodelphis VLCVPLARNIYGLIAPNFGIGFAIGMVDSS
Gallus ILCVPFAKNIYGLIAPNFGVGFAIGMVDSS
Tetraodon VICVPFATSIYGLILPNFGVGFAIGMVDSS
Danio ILCVPLAKDIYGLIVPNFGVGFAIGMVDSS
Drosophila LIFIPMATSITHLIIPNAGLGFAIGMVDSS
C. elegans LLSIPSATSVAGLIIPHALLGFSIGMIDAS
hVMAT1 LLCVPLAHNIFGLIGPNAGLGLAIGMVDSS

Figure 1 (facing page). The Causative Defect.
Panel A depicts the family pedigree. Squares denote male family members, circles female family members, black symbols affected family members, and diamonds miscarriages; double bars indicate consanguineous marriages, and the arrow indicates the index patient. Panel B shows the homozygous haplotype shared by the affected persons. Panel C shows electropherograms of a portion of *SLC18A2* containing the mutation. Panel D depicts the vesicular monoamine transporter 2 (VMAT2) protein within the synaptic vesicle membrane; the arrow indicates the mutated proline. Panel E shows the primary sequence of the portion of human VMAT2, which in our patients contains the mutated proline, and corresponding sequences in various orthologues and in the VMAT1 paralog of neuroendocrine cells. TM9 and TM10 are parts of the 9th and 10th transmembrane domains, respectively, of VMAT2. Panel D adapted from Erickson and Eiden.[14]

lasting hours. Video electroencephalographic monitoring had ruled out seizures, and a symptom-based diagnosis of oculogyric crisis had been made. Development had been normal initially but had slowed after presentation. The girl sat at 30 months, crawled at 4 years, and walked at 13 years.

At 16 years of age, she had fatigue, excessive diaphoresis, profuse nasal and oropharyngeal secretions, noisy breathing, hypernasal speech, poor distal perfusion, cold hands and feet, disrupted sleep, hypotonia, dysarthria, and ataxia. There was no diurnal variation and no improvement with administration of vitamin B_6 or folinic acid. Neurologic examination revealed ptosis, hypomimia, facial dyskinesia, and limited upward gaze. She had axial hypotonia and appendicular hypertonia specifically involving extensor muscles of the arms and legs. Her deep-tendon reflexes were minimally hyperreflexic, and her plantar responses were flexor. Coordination testing revealed a fine tremor and dysdiadochokinesia in the arms and legs. The patient's gait was parkinsonian, with typical shuffling; her posture was stooped, and her postural reflexes were diminished. She walked with bilateral alternating dystonia of the hands and feet, with intermittent toe walking and foot inversion, and was unable to perform a tandem walk.

Results of basic blood tests, metabolic screening tests (Table S2 in the Supplementary Appendix), repeat video electroencephalography, magnetic resonance imaging, and magnetic resonance spectroscopy were normal. A lumbar puncture was performed in a 2-year-old affected sibling, and analysis of the CSF showed normal levels of neurotransmitter metabolites, intermediates, and precursors (Table S3 in the Supplementary Appendix). However, urinary neurotransmitter testing revealed elevated levels of monoamine metabolites (5-hydroxyindoleacetic acid, 17.6 μg per deciliter [reference range, 0 to 6.0]; homovanillic acid, 14.1 μg per milligram of urinary creatinine [reference range, 0 to 13.4]) and decreased levels of measurable monoamines (norepinephrine, 1 μg per deciliter [reference range, 4 to 29]; dopamine, 19 μg per deciliter [reference range, 40 to 260]) (Table S3 in the Supplementary Appendix).

On the basis of the parkinsonism and the diminished urinary dopamine, the proband and three younger affected siblings were given levodopa–carbidopa, which within 1 week resulted in major deterioration, with the appearance of intense chorea and worsened dystonia. Discontinuation of the medication led to a rapid return to baseline function in all four children.

METHODS

GENETIC STUDIES

The study was approved by the research ethics board of the Hospital for Sick Children, and parents provided written informed consent. We genotyped more than 300,000 single-nucleotide polymorphisms (SNPs) in eight family members, V-3, V-4, V-6, V-7, V-8, V-9, V-10, and VI-2 (Fig. 1A) (with the use of an Illumina 300K SNP microarray), followed by homozygosity mapping to identify the homozygous loci shared by the affected children. A subset of 2500 SNPs with a minimal allele frequency greater than 0.4 in the population genotyped as part of the international HapMap study and with average spacing of approximately 1.0 Mb was selected for parametric linkage analysis. We used Sanger sequencing of candidate gene exons to identify the mutation, whole-exome sequencing (Agilent V4 50Mb capture kit and Illumina HiSeq 2000 sequencing) to rule out other mutations, and TaqMan genotyping to confirm the absence of the mutation in controls.

FUNCTIONAL ANALYSIS OF P387L-MUTANT VMAT2

We engineered a construct encoding VMAT2 that contained the P387L substitution, and we carried out an assay of vesicular serotonin uptake in a heterologous cell system (see the Methods section in the Supplementary Appendix). Transport mediated by VMAT2 was measured by incubating membrane preparations with tritiated serotonin, followed by rapid washing and filtration to retain vesicles with trapped substrate.

RESULTS

MUTATION IDENTIFICATION

Homozygosity mapping identified a single homozygous 3.2-Mb interval on chromosome 10q in the region of 10q25.3-26.11 that was shared by five affected family members but not by unaffected members (Fig. 1B). Parametric linkage analysis revealed a significant logarithm of odds (lod) score of 4.1 in this region. Another locus, on chromosome 3, yielded a significant lod score of 3.1 but did not correspond to a region of shared homozygosity. We sequenced exons and exon–intron boundaries of eight genes known to have neuronal functions and observed a novel variant (c.1160C→T) in exon 13 (Fig. 1C), which is predicted to result in a substitution of leucine for proline at position 387 (p.P387L) in VMAT2. The variant was homozygous in affected family members but not in 78 unaffected members, 26 of whom carried the variant in the heterozygous state.

We also performed whole-exome sequencing in the proband, which independently identified the *SLC18A2* change and revealed no other novel nonsynonymous variant in the linked region of shared homozygosity. *SLC18A2* c.1160C→T is not present in data sets of sequenced genomes, including the 1000-genome database. In addition, screening for *SLC18A2*, one of the most extensively studied candidate genes for involvement in Parkinson's disease, was previously performed in 704 healthy persons of diverse ethnic backgrounds and 452 patients with Parkinson's disease,[11-13] none of whom had the c.1160C→T change. Collectively, these results suggest that *SLC18A2* c.1160C→T is the causative defect in this family.

FUNCTIONAL CHARACTERIZATION OF P387L-MUTANT VMAT2

SLC18A2 encodes the VMAT2 protein located in membranes of monoamine synaptic vesicles (Fig. 1D, 2A, and 2B). Proline residues adjacent to transmembrane segments have major structural effects and are overrepresented among residues subject to disease-causing substitutions.[15] The proline residue in the 387 position (Pro387) of the VMAT2 protein is adjacent to a transmembrane segment (Fig. 1D). Sequence alignment shows that Pro387 is highly conserved through evolution and thus suggests that its substitution is likely to be deleterious. It is also conserved in the paralogous protein VMAT1 and in the *Caenorhabditis elegans* CAT-1 protein — the single vesicular monoamine transporter in nematodes (Fig. 1E).[16] The residue is not conserved in the vesicular acetylcholine transporter, which maintains 39% identity with VMAT2; this finding implies that Pro387 may have a specific role in monoamine transport.

To determine the effect of the P387L mutation on VMAT2 transport activity, we transiently and separately expressed nonmutant and mutant human VMAT2 in COS-7 cells. Immunoblot analysis of membrane preparations confirmed equivalent levels of mature glycosylated VMAT2 in parallel transfections, suggesting that there was no major defect in protein processing. However, P387L-mutant VMAT2 showed dramatically decreased activity as compared with nonmutant VMAT2 (Fig. 2C). Use of the specific VMAT inhibitor reserpine confirmed that P387L-mutant VMAT2 still exhibited some weakly measurable uptake (Fig. 2D). Thus, the P387L mutation results in severe, but not complete, loss of function.

TREATMENT

Defective monoamine loading into synaptic vesicles, and therefore neurotransmission, was consistent with symptoms of monoamine deficiency in affected members of the family, despite their normal levels of brain monoamine. With this insight, we gave the proband a direct dopamine-receptor agonist (pramipexole), which resulted, within 1 week, in dramatic and sustained disappearance of parkinsonism and dystonic attacks and improvement in other symptoms (Table 1). We then provided treatment to the younger siblings, who also had improvement. It seemed that the younger the affected child, the more substantial the recovery (Table 1). The affected children are now in their 32nd month of treatment, with continuing benefits and minimal side effects (slight overactivity and weight loss).

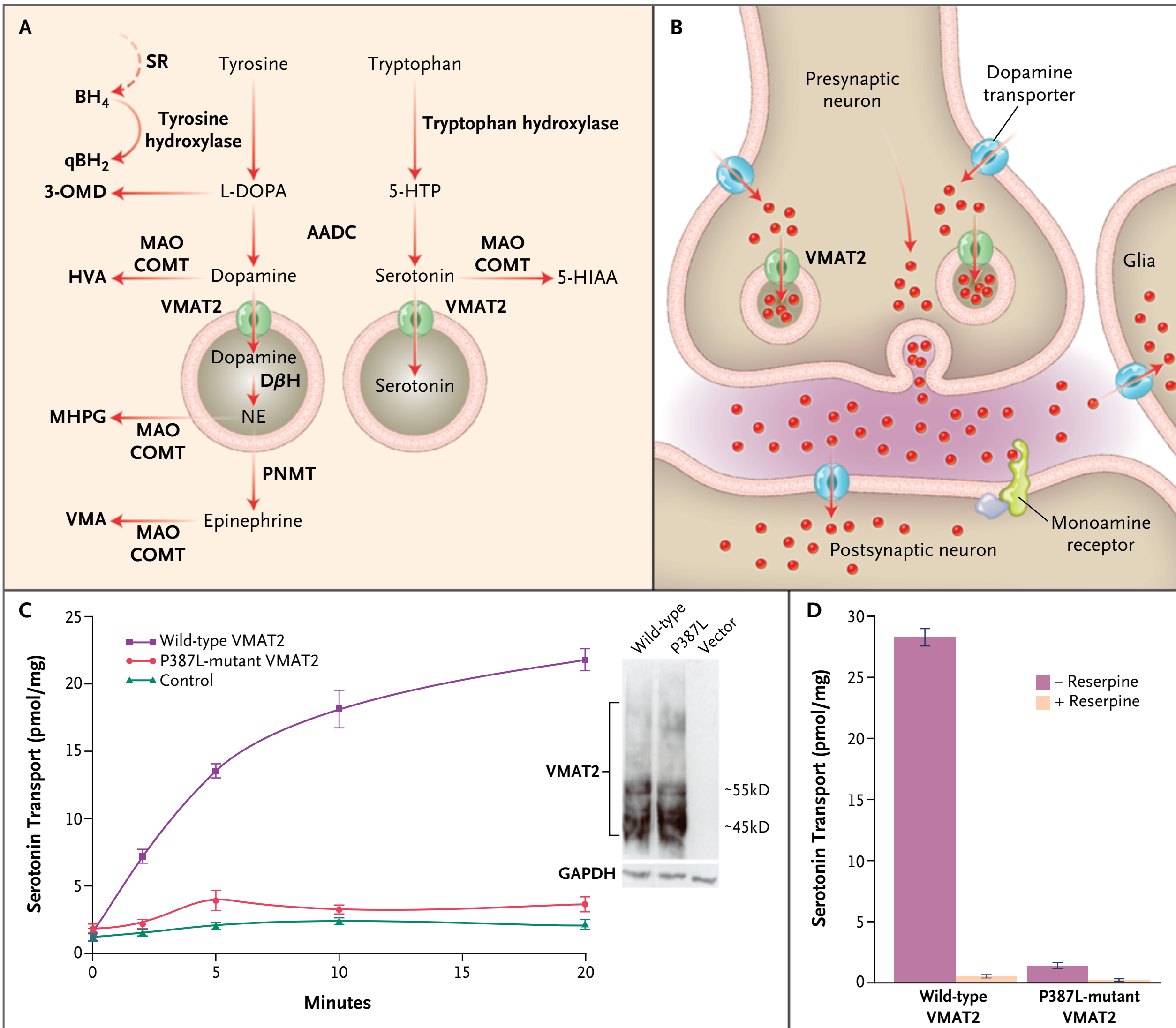

Figure 2. Monoamine Metabolism, Vesicular Loading, Synaptic Transmission, and the Loading Defect in the Patients.

Panel A summarizes the metabolism of monoamines and their transport into synaptic vesicles; norepinephrine (NE) and epinephrine are synthesized from dopamine within the vesicle. Panel B depicts monoamine neurotransmission; the site of action of the dopamine agonist in the patients described here is at the postsynaptic neuron membrane. Panel C shows the time course of tritiated serotonin uptake into vesicles prepared from COS-7 cells transfected with wild-type or mutant (P387L) human VMAT2 or with the vector alone (control). Western blot analysis showed equivalent VMAT2 levels and post-translational processing in assay lysates. Panel D shows the uptake of tritiated serotonin (over a period of 10 minutes) by vesicles prepared from cells transfected with wild-type or P387L-mutant VMAT2, with and without the addition of 10 μM of the specific VMAT inhibitor reserpine. AADC denotes aromatic L-amino acid decarboxylase, BH_4 tetrahydrobiopterin, COMT catechol-O-methyltransferase, DβH dopamine β-hydroxylase, GAPDH glyceraldehyde-3-phophate dehydrogenase, HIAA hydroxyindoleacetic acid, HTP hydroxytryptophan, HVA homovanillic acid, MAO monoamine oxidase, MHPG 3-methoxy-4-hydroxyphenylglycol, OMD O-methyldopa, PNMT phenylethanolamine N-methyltransferase, qBH_2 quinonoid dihydrobiopterin, SR sepiapterin reductase, and VMA vanillylmandelic acid.

DISCUSSION

The mutation in *SLC18A2* that we describe here is expected to affect monoamine neurotransmission and thus result in a phenotype that has overlap with all monoamine disorders. Because movement disorder is conspicuous among symptoms of monoamine disturbance, the clinical picture of the disease that we describe is closest to that of diseases affecting dopamine — chiefly, deficien-

Table 1. Relationship between Age at Initiation of Dopamine-Agonist Therapy and Disease Course in the Four Affected Siblings.

Variable	Age at Initiation of Therapy			
	Patient V-6, 18 yr	Patient V-9, 11 yr	Patient V-10, 7 yr	Patient V-11, 3 yr
Cognition and ability to learn	Mildly improved	Mildly improved	Moderately improved	Greatly improved; patient able to make stories from pictures
Oculogyric crises	No further events; patient required higher dose by weight than her siblings	No further events	No further events	No further events
Dystonia	Gait dystonia persisted	Gait dystonia persisted	Gait dystonia persisted	Gait dystonia improved
Parkinsonism	Improved	Improved	Improved	Improved
Fine motor skills	Improved coordination; patient able to feed self, drink from cup, and hold a pen; improved handwriting	Improved coordination; patient learning to hold a pen, unable to write or read	Patient learning to hold a pen and drink from a cup independently, unable to write or read	Patient able to write, learning to read
Language and speech	Dysarthria	No language development	Patient could say "Mama" and "Papa"	Normal language development and mild dysarthria
Gait	Improved posture and reduced fatigue (patient had started walking at 13 yr of age)	Patient started walking within days after treatment	Patient started walking within days after treatment	Patient started walking within days after treatment

cies in dopamine transporter, tetrahydrobiopterin, tyrosine hydroxylase, and aromatic L-amino acid decarboxylase (AADC) (Fig. 2A and 2B). The phenotype of the affected siblings has particular similarity to AADC deficiency in that it improves with direct dopamine agonism but not with levodopa, although the siblings had greater improvement than that typically observed in those with AADC deficiency treated with dopamine agonists, and rather than having a lack of response to levodopa, the siblings had a worsening of symptoms. Two other features that distinguish the disease we describe here from AADC deficiency are the lack of improvement with the AADC enzyme cofactor vitamin B_6 and the absence of worsening in the evening, which in AADC deficiency is the result of neurotransmitter depletion due to insufficient production.[1,4,7,8]

The standard diagnostic test in patients with suspected diseases of monoamine metabolism is the measurement of monoamine metabolites in the CSF. Because each specific defect results in a particular metabolite profile, this single test specifies the disease.[2,3,6] Analysis of monoamines or their metabolites in urine is not reliable for the diagnosis of monoamine neurotransmitter diseases,[2,3,6] except for one — AADC deficiency — in which increased 3-O-methyldopa with decreased vanillylmandelic acid (Fig. 2A) in the proper clinical context is highly suggestive and generally confirmed by mutation analysis.[1,4,7,8] In the present condition, the urine shows abnormalities because VMAT2 also functions at sites outside the central nervous system, including the peripheral nervous system, adrenal medulla, and platelets.[17] Our detection of abnormalities in the urine but not the CSF may reflect differences in monoamine and metabolite stabilities, processing, and normal ranges between the brain and the periphery. In any case, it appears that AADC and VMAT2 deficiencies, which are metabolically and clinically similar disorders, could be screened for by urine testing and then confirmed by gene sequencing, thus obviating the need for a lumbar puncture.

Direct characterization of the mutant VMAT2 protein in this study revealed a severe detriment of vesicular transporter function, which could be due to poor incorporation of the transporter into vesicle membranes or to loss of activity. Proline-to-leucine substitutions are generally considered to be deleterious to organismal fitness,[18,19] on the basis of analyses of amino acid substitutions in evolutionarily conserved proteins, and to be damaging to protein function, owing to a physicochemical difference.[20] Proline places unique constraints on the flexibility of the peptide backbone, particularly with respect to insertions of adjacent transmembrane segments.[15]

A complete knockout of *Slc18a2* in mice results in a lack of exocytotic monoamine neurotransmission; the mutant animals feed poorly and die within days after birth.[21,22] By contrast, mice that express just 5% native Vmat2 levels live to adulthood and have minor age-related motor deficits over time.[23] The phenotypic spectrum of Vmat2 deficiency in mice is therefore broad and consistent with a requirement for large decreases in protein function to cause severe motor symptoms.

We found that the motor phenotype was correctable and that the extent of correction appeared to depend on the stage of the disease. If true, this dependency could be due to irreversibly perturbed reorganization of dopamine pathways in brains subjected to chronic deficiencies in monoamine neurotransmission during active brain development. Although the improvement in the patients in this study was striking, it was not complete, probably because of monoamine deficiency during development and also because of ongoing deficiencies of the non-dopamine amines and impairment in regulated release of dopamine.

Heterozygous mice with a single *Slc18a2* allele have no motor phenotype but do have a depressive behavioral phenotype.[24] We found a very high rate of depression among the parents of our patients (all five of the five parents interviewed reported depression). This is also seen in parents of patients with AADC deficiency and is thought to be caused by clinically significant reductions in serotonin in these persons with hemizygous defects in the serotonin pathway.[1,4,7,8] To what extent mutations in the genes encoding AADC and VMAT2 may contribute to common depression and its heritability remains to be seen.

The initial selection of treatment of the affected children on the basis of clinical phenotype alone (parkinsonism) led to severe, immediate worsening of the movement disorder. This was probably caused by the known toxicity of elevated levels of dopamine, in particular to dopaminergic neurons.[25] Subsequent identification of the underlying pathophysiology allowed the rational selection of an appropriate treatment. A related severe disorder, sepiapterin reductase deficiency (see Fig. 2A), was recently diagnosed by means of whole-genome sequencing in 14-year-old fraternal twins; this previously known disorder had been undiagnosed (and therefore untreated) for many years because of the difficulties in obtaining a precise diagnosis for rare diseases.[26] Diagnosis allowed treatment of the disorder, which led to recovery in those children.

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