RESEARCH ARTICLE

Movement Disorders in Adult Surviving Patients with Maple Syrup Urine Disease

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ABSTRACT: Maple syrup urine disease is a rare metabolic disorder caused by mutations in the branched-chain α-keto acid dehydrogenase complex gene. Patients generally present early in life with a toxic encephalopathy because of the accumulation of the branched-chain amino acids leucine, isoleucine, and valine and the corresponding ketoacids. Movement disorders in maple syrup urine disease have typically been described during decompensation episodes or at presentation in the context of a toxic encephalopathy, with complete resolution after appropriate dietary treatment. Movement disorders in patients surviving childhood are not well documented. We assessed 17 adult patients with maple syrup urine disease (mean age, 27.5 years) with a special focus on movement disorders. Twelve (70.6%) had a movement disorder on clinical examination, mainly tremor and dystonia or a combination of both. Parkinsonism and simple motor tics were also observed. Pyramidal signs were present in 11 patients (64.7%), and a spastic-dystonic gait was observed in 6 patients (35.2%). In summary, movement disorders are common in treated adult patients with maple syrup urine disease, and careful neurological examination is advisable to identify those who may benefit from specific therapy. © 2011 *Movement* Disorder Society

Key Words: maple syrup urine disease; metabolic; movement disorders; dystonia; parkinsonism

Maple syrup urine disease (MSUD, OMIM #248600) is a rare inborn error of metabolism caused by a deficiency in the activity of the branched-chain α-keto acid dehydrogenase (BCKD) complex. As a consequence, the degradation of the 3 branched-chain amino acids (BCAAs) leucine, isoleucine, and valine is blocked after the first catabolic step (transamination), resulting in accumulation of BCAAs and the corresponding branched-chain α-keto acids (BCKAs) in biological fluids.

MSUD is inherited as an autosomal recessive disorder, and its worldwide frequency is estimated as 1:185,000,[1] although in the Mennonite population of Lancaster and Lebanon counties in Pennsylvania its frequency is higher, with a prevalence of approximately 1 in 176 newborns.[2]

The human BCKD complex is a multienzymatic macromolecule composed of 3 catalytic subunits (E1, with an $\alpha_2\beta_2$ structure, E2, and E3) encoded by different genes located on chromosomes 19, 6, 1, and 7, respectively. Mutations in each of these loci are responsible for different molecular phenotypes indicated as type IA (E1α), type IB (E1β), type II (E2), and type III (E3).[1] Depending on the clinical presentation and the residual enzymatic activity of BCKD, 5 phenotypes are recognized: classic, intermediate, intermittent, thiamine responsive, and E3 deficient.[1,3] Classic MSUD is the most common form, and affected newborns

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TABLE 1. Demographic features of MSUD patients

Patient number	Sex	Age	Movement disorder	Disease duration (y)	Diet	Daily protein intake (g)
1	F	23	Y	23	Y	5
2	M	27	Y	27	Y	5.5
3	M	18	N	18	Y	8
4	F	31	N	31	Y	8
5	F	17	Y	17	Y	8
6	F	25	Y	25	Y	8
7	F	33	Y	33	Y	10
8	F	27	N	27	Y	10
9	M	20	Y	20	Y	11
10	F	31	Y	31	Y	12
11	M	33	Y	33	Y	12
12	F	48	Y	48	Y	18
13	M	26	Y	26	Y	12
14[a]	F	30	N	28	N	Unrestricted
15[a]	M	25	Y	23	N	Unrestricted
16[a]	F	25	Y	25	N	Unrestricted
17[a]	F	29	N	25	N	Vegetarian
Total	11 F 6 M	27.5 (mean)	12 Y 5 N	27 (mean)	11 Y 6 N	9.8 (mean)

[a]Nonclassic MSUD patients.

present with lethargy, poor sucking, and rapidly progressive encephalopathy in the first days of life, when the characteristic odor of burnt sugar may be noted. Alterations of muscular tone and abnormal dystonic extensions of the arms can occur during this stage of disease.[4] Increased blood, urine, and cerebrospinal fluid BCAAs (especially leucine) are found during acute metabolic decompensation, often provoked by intercurrent illness, fasting, injury, or surgery and contributed to by endogenous protein catabolism.

Patients with MSUD later on may develop neurological sequelae such as spasticity and quadriplegia as a consequence of the damage resulting from widespread cerebral edema at first clinical presentation or during decompensation episodes.[5]

Movement disorders can be part of the manifestations of various metabolic diseases,[6] alone or in combination with other neurological findings. An increasing number of individuals with MSUD are surviving childhood thanks to a BCAA-restricted diet, but little information on the prevalence of movement disorders in these adults is available. We present the clinical neurological findings of 17 adult patients with MSUD, with a particular emphasis on the spectrum of movement disorders.

Patients and Methods

Seventeen patients (11 women, 6 men; mean age, 27.5 years) diagnosed with MSUD followed up at the Charles Dent Metabolic Unit, National Hospital for Neurology and Neurosurgery, London, were reviewed. This is a tertiary adult referral centre with close links to the pediatric service where patients with MSUD are followed up until age 16 after initial diagnosis.

Relevant details about patients' medical history were obtained from their files and by direct questioning of either the patients themselves or their caregivers. All patients underwent a full neurological examination by a single neurologist, along with metabolic follow-up including determination of plasma BCAAs.

Thirteen patients were diagnosed with classic, 2 with intermittent, and 2 with intermediate MSUD. Disease duration at the time of examination ranged from 17 to 48 years (mean, 27 years), and all but 2 classic cases were diagnosed within the first 3 weeks of life. The 4 nonclassic cases were diagnosed between 2 and 4 years of age. In all patients, the diagnosis of MSUD was based on clinical suspicion and confirmed by measuring elevated BCAA levels in blood and urine. Genetic analysis was not routinely included in the diagnostic workup. One Ashkenazi Jewish patient was tested on a research basis and was found to carry a previously described homozygous mutation (c.548G>C, p.Arg183Pro) in exon 5 of the *BCKDHB* gene, encoding the E2-β subunit of the BCKD complex.

Patients with classic MSUD were all on a protein-restricted diet (mean protein intake, 9.8 g/day) and amino acid supplementation, whereas 3 of the 4 nonclassic cases were on an unrestricted diet, and 1 followed a vegetarian diet.

Demographic data of the patients are shown in Table 1.

Results

Twelve of 17 patients (70.6%) had a movement disorder detectable on clinical examination. Tremor was

TABLE 2. Neurological findings in adult patients with MSUD

Clinical finding	Type	Number (percentage)
Movement disorders (12 of 17 patients)	Tremor	7 (41.1%)
	—At rest	3
	—Postural	5
	—Intention	2
	Dystonia	6 (35.3%)
	—Cervical	2
	—Upper limbs	5
	—Lower limbs	3
	Parkinsonism	3 (17.6%)
	Other movement disorders	1 (5.9%)
Other neurological findings (11 of 17 patients)	Pyramidal signs	11 (64.7%)
	Scissoring-dystonic gait	6 (35.2%)
	Language impairment	6 (35.2%)
	Neuropsychiatric disturbances	2 (11.7%)
	Cognitive impairment	10 (58.8%)
	Epilepsy	4 (23.5%)

present in 7 subjects (41.1%), alone (1 case) or in combination with other movement disorders: dystonia in 6 (35.3%), parkinsonism in 3 (17.6%; see Video Segment 3), and simple motor tics in 1 (5.9%). Among the patients with a movement disorder (n = 11), tremor and dystonia were the most common findings on examination, being detected in 63.6% and 54.5% of subjects, respectively. Of these, 3 patients (27.2%) exhibited a tremor at rest (asymmetric in 2 cases, symmetric in 1 case), 5 patients (45.5%) a postural tremor, and 2 patients (18%) an intention tremor. Among patients with dystonia, 5 (45.5%) had a dystonic posture affecting the hands and 3 (27.2%) the feet, presenting as bilateral plantar flexion and inversion in 1 case and as part of a scissoring-dystonic gait in 2 cases (see Video Segments 1 and 2), and 2 cases (18%) displayed cervical dystonia. Four of 5 patients with dystonia also had a tremor in the affected part of the body, suggesting a dystonic tremor. All patients with parkinsonism presented bradykinesia on finger tapping (symmetric in 1 patient, asymmetric in 2 patients) with no rest tremor. One patient showed additional features including facial hypomimia and poverty of movements, loss of postural reflexes, and bilateral reduction of arm swings, along with cogwheel rigidity in the left upper limb.

In 1 case simple motor tics were detected on examination, manifesting as brief neck rotations to the left, which were partially suppressible with distraction, but we cannot exclude that this finding was incidental. In all patients the distribution of movement disorders was in the upper part of the body, with additional involvement of the lower limbs in 3 cases. Table 2 summarizes the movement disorders found in the patients examined.

In addition to movement disorders, pyramidal signs such as brisk reflexes and spasticity were frequent on examination, overall being present in 11 patients (64.3%). Six showed a scissoring-dystonic gait and were significantly disabled. Language impairment was present in 6 of 17 patients (35.2%), including spastic dysarthria in 4 and slurred speech in 2. Four patients (23.5%) had epilepsy that required pharmacological treatment. Neuropsychiatric disturbances including depression and obsessive-compulsive disorder were present in 2 subjects (11.7%), whereas various degrees of learning difficulties with mental retardation were shown in 10 of 17 cases (58.8%).

Discussion

In this observational study, we describe the spectrum of movement disorders in adults with MSUD. MSUD is a rare metabolic disorder that generally presents with a toxic encephalopathy within the first days of life. Long-term outcomes in treated adult patients have been difficult to establish because of the rarity of the disorder and its severity on initial presentation, often leading to premature death. It is well recognized that various movement disorders can be present in metabolic conditions, often being secondary to early cerebral damage,[3] but the spectrum of movement disorders in MSUD is unknown. Although we have previously described neuropsychometric outcomes in some patients included in this study,[7] no detailed studies have been published on long-term motor signs.

In our series of 17 patients, more than two thirds exhibited a movement disorder on clinical examination, mainly tremor and dystonia or a combination of both. These were present in the upper limbs in all cases, with additional involvement of the neck in 2 patients and of the lower limbs in 3 patients. Aside from movement disorders, the most common neurological findings were pyramidal signs in the lower limbs and learning difficulties, observed in 64.7% and 58.8% of cases, respectively. The combination of dystonia and spasticity in the lower limbs was the most disabling clinical finding, significantly reducing patients' ability to walk independently and thus interfering with their quality of life.

To date, movement disorders in MSUD have only been described as part of the symptoms at onset in the context of a toxic encephalopathy, as recurrent paroxysmal ataxia or paroxysmal dystonia in intermittent variant MSUD, and during episodes of decompensation.[1,8,9] In these cases, movement disorders tended to resolve after appropriate dietary treatment.

In our series of adult patients, many had a persistent movement disorder, even when on a strict dietary regimen in the absence of intercurrent metabolic decompensation. Interestingly, we did not observe major cerebellar signs such as ataxia, as previously reported,[3] at presentation or during decompensation episodes

consistent with a typical severe cerebellar edema seen on neuroimgaing[10] and with prominent neuropathological alterations in the cerebellum.[1]

There is considerable interest in movement disorders due to metabolic diseases, as this can provide some answers with regard to pathophysiology, as recently exemplified by Gaucher's disease–related parkinsonism. Our clinical observations raise the question of the nature of the underlying pathophysiology of movement disorders seen in adult MSUD patients. With regard to the neuropathology, it is known that in MSUD considerable neuronal loss is present in the pontine nuclei and substantia nigra,[11] and striatal damage has been demonstrated both in the animal model of MSUD[12] and in affected children.[4]

Moreover, leucine has a high affinity for the L1-neutral amino acid transporter through which other amino acids are transported into the central nervous system; therefore, high leucine plasma concentrations reduce the uptake of some amino acids in the brain, including phenylalanine, tyrosine, and tryptophan. This leads to the depletion of some neurotransmitters in the brain such as dopamine and serotonin, as demonstrated in the animal model of MSUD by Zinnanti et al,[13] who observed a reduction in dopamine levels in the brain of MSUD mice by more than 60% along with decreased GABA and glutamate levels. The depletion of neurotransmitters, especially dopamine, was concomitant with the initiation of limb dystonia and gait abnormalities in MSUD mice.

Although these findings were described during acute encephalopathy, it is possible that altered neurotransmitter levels, especially dopamine, are present as a long-term consequence in the brains of adult MSUD patients, being responsible for the development of dystonia, as seen in other diseases characterized by reduced dopamine availability (juvenile Parkinson's disease, dopa-responsive dystonia).[14,15] Interestingly, in a series of 36 infants, dystonia was observed at onset in 42.2% of patients, being associated with high serum leucine-to-tyrosine ratios and thus further suggesting that acute leucinosis with secondary tyrosine deficiency may contribute to the development of dystonia.[4]

Finally, the development of movement disorders in MSUD mice has been further explained by a disruption of the cerebral energy metabolism from the toxic effect of BCKA in the central nervous system with reduced ATP and phosphocreatine levels,[13] which may affect the normal functioning of basal ganglia and other parts of the brain highly dependent on the mitochondrial respiratory chain.

In addition to these neurochemical changes that may at least be partly responsible for the movement disorders observed in our patients, the permanent damage resulting from early encephalopathy at onset is likely to play a role in the development of movement disorders. In this regard, 3 of our patients with a movement disorder (parkinsonism; rest tremor; dystonia and spastic-dystonic gait) underwent a brain MRI scan that did not show any abnormality of either the basal ganglia or the cerebellum. However, we cannot exclude that other patients included in our series might have a structural damage on neuroimaging.

It may be that given the above-mentioned biochemical alterations, the development of movement disorders in MSUD is associated with the number as well as the severity of decompensation episodes. However, in our series it was not possible to clearly define the total number of decompensation episodes throughout life, as not all resulted in hospital admission or were clearly documented.

With regard to the treatment of movement disorders, symptomatic drugs such as local botulinum toxin injections in patients with dystonia or dopaminergic drugs in those with parkinsonism should be considered as potential treatments in the future. No cases of deep brain stimulation (DBS) in patients with MSUD and movement disorder have been reported so far, but DBS has been successfully used in a few cases of other inborn errors of metabolism also presenting with movement disorders such as Lesh-Nyhan syndrome.[16,17]

Conclusions

Movement disorders have been described in MSUD at onset or during decompensation episodes, mainly as paroxysmal dystonia or ataxia. In this study, we assessed 17 adult patients with MSUD and observed a high prevalence of movement disorders, even in patients with a long disease duration following a protein-restricted diet and under relatively stable metabolic control. Dystonia in the upper limbs and tremor were the most frequent findings. We speculate that these symptoms may be secondary to cerebral damage from toxic encephalopathy at onset and during recurrent acute decompensation and/or chronic reduced levels of neurotransmitters, such as dopamine, as demonstrated in the animal model of MSUD.

Our findings suggest that a careful neurological assessment is advisable in adult patients with MSUD, and we recommend screening these patients for movement disorders such as dystonia and parkinsonism, as these symptoms are potentially treatable. Further studies are needed to clarify the pathophysiology of movement disorders in MSUD in order to offer patients specific treatments to improve their quality of life. ■

Legends to the Video

Video Segment 1. Seventeen-year-old patient. Dystonic posture of feet (inversion) with gait showing

mixed dystonia and spasticity. Cervical dystonia (left torticollis, mild retrocollis, and left shoulder elevation). Mild dystonic posture of the right hand, with slowness in performing finger tapping bilaterally without evidence of clear decrement.

Video Segment 2. Thirty-one-year-old patient. Dystonic posture of feet and toes and a gait with a mixture of dystonia and spasticity. A bilateral dystonic posture of both hands, more marked on the right side, is visible on walking and keeping arms outstretched. Mild cervical dystonia (right torticollis) is also detectable.

Video Segment 3. Thirty-year-old patient. Slow gait with reduced arm swings bilaterally. Hypomimia, poverty of movements, and left bradykinesia on finger tapping.

References

1. Chuang DT, Shih VE. Maple syrup urine disease (branched-chain ketoaciduria). In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The Metabolic and Molecular Bases of Inherited Disease. New York, McGraw-Hill; 2001:1971–2006.
2. Marshall L, Di George A. Maple Syrup urine disease in the old order Mennonites. Am J Hum Gen. 1981;33:139A.
3. Simon E, Flaschker N, Schadewaldt P, Langenbeck U, Wendel U. Variant maple syrup urine disease (MSUD) - the entire spectrum. J Inherit Metab Dis. 2006;29:716–724.
4. Morton DH, Strauss KA, Robinson DL, Puffenberger EG, Kelley RI. Diagnosis and treatment of maple syrup disease: a study of 36 patients. Pediatrics. 2002;109:999–1008.
5. Naughten ER, Jenkins J, Francis DE, Leonard JV. Outcome of maple syrup urine disease. Arch Dis Child. 1982;57:918–921.
6. Gouider-Khouja N, Kraoua I, Benrhouma H, Fraj N, Rouissi A. Movement disorders in neuro-metabolic diseases. Eur J Paediatr Neurol. 2010;14:304–307.
7. le Roux C, Murphy E, Hallam P, Lilburn M, Orlowska D, Lee P. Neuropsychometric outcome predictors for adults with maple syrup urine disease. J Inherit Metab Dis. 2006;29:201–202.
8. Morris MD, Lewis BD, Doolan PD, Harper HA. Clinical and biochemical observations on an apparently nonfatal variant of branched-chain ketoaciduria (maple syrup urine disease). Pediatrics. 1961;28:918–923.
9. Temudo T, Martins E, Poças F, Cruz R, Vilarinho L. Maple syrup disease presenting as paroxysmal dystonia. Ann Neurol. 2004;56:749–750.
10. Steinlin M, Blaser S, Boltshauser E. Cerebellar involvement in metabolic disorders: a pattern-recognition approach. Neuroradiology. 1998;40:347–354.
11. Kiil R, Rokkones T. Late manifesting variant of branched-chain ketoaciduria (maple syrup urine disease). Acta Paediatr. 1964;53:356–364.
12. Hauber W. Involvement of basal ganglia transmitter systems in movement initiation. Prog Neurobiol. 1998;56:507–540.
13. Zinnanti WJ, Lazovic J, Griffin K, et al. Dual mechanism of brain injury and novel treatment strategy in maple syrup urine disease. Brain. 2009;132:903–918.
14. Khan NL, Graham E, Critchley P, et al. Parkin disease: a phenotypic study of a large case series. Brain. 2003;126:1279–1292.
15. Trender-Gerhard I, Sweeney MG, Schwingenschuh P, et al. Autosomal-dominant GTPCH1-deficient DRD: clinical characteristics and long-term outcome of 34 patients. J Neurol Neurosurg Psychiatry. 2009;80:839–845.
16. Cif L, Biolsi B, Gavarini S, et al. Antero-ventral internal pallidum stimulation improves behavioral disorders in Lesch-Nyhan disease. Mov Disord. 2007;22:2126–2129.
17. Taira T, Kobayashi T, Hori T. Disappearance of self-mutilating behavior in a patient with lesch-nyhan syndrome after bilateral chronic stimulation of the globus pallidus internus. Case report. J Neurosurg. 2003;98:414–416.