Eye Movement Disorders and Neurological Symptoms in Late-Onset Inborn Errors of Metabolism

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Abstract: Inborn errors of metabolism in adults are still largely unexplored. Despite the fact that adult-onset phenotypes have been known for many years, little attention is given to these disorders in neurological practice. The adult-onset presentation differs from childhood-onset phenotypes, often leading to considerable diagnostic delay. The identification of these patients at the earliest stage of disease is important, given that early treatment may prevent or lessen further brain damage. Neurological and psychiatric symptoms occur more frequently in adult forms. Abnormalities of eye movements are also common and can be easily overlooked in a general examination. In adults with unexplained psychiatric and neurological symptoms, a special focus on examination of eye movements can serve as a relatively simple clinical tool to detect a metabolic disorder. Eye movements can be easily quantified and analyzed with video-oculography, making them a valuable biomarker for following the natural course of disease or the response to therapies. Here, we review, for the first time, eye movement disorders that can occur in inborn errors of metabolism, with a focus on late-onset forms. We provide a step-by-step overview that will help clinicians to examine and interpret eye movement disorders.

Key Words: eye movement disorders; inborn errors of metabolism; movement disorders; adult-onset

Inborn errors of metabolism (IEM) are a heterogeneous group of genetic disorders that cause dysfunction of an enzyme or transporter involved in cellular metabolism. Historically, inborn errors were thought to be rare, occurring in less than 1 per 100,000 live births and to only present during infancy or early childhood. We now know that this prevalence is an underestimate, and that IEM present in adolescence or adulthood much more often than previously thought. Retrospective data from an ethnically diverse population in the United...
Kingdom (1999-2003) revealed an overall prevalence of metabolic disease of 1 per 784 live births; mitochondrial diseases, lysosomal storage diseases, and amino acid disorders were most frequent. Furthermore, more than one quarter of all diagnoses were made after the age of 15 years. Adult phenotypes may differ from the classic childhood-onset phenotypes. In adulthood, many IEM patients present with neurological or psychiatric symptoms, but considering an IEM in the differential diagnosis of an adult patient is still uncommon among neurologists. Missing or delaying diagnosis of an IEM can have important implications. In particular, patients with a milder phenotype appear to benefit most from timely treatment, so identifying them is important to prevent further (neurological) damage.

Whereas the neurological symptoms in patients with IEM often involve various types of movement disorders, eye movement disorders are also frequently observed and can be an important diagnostic clue. The type of eye movement disorder can often further delineate the type of IEM.

The aim of this article is to review the abnormalities of eye movements that can be observed in IEM, with an emphasis on those IEMs that can present later in life. Our goal is to increase awareness of eye movements in adult patients with movement disorders and other neurological or psychiatric disturbances because they can be the key to early diagnosis. Because more types of IEM are being identified that can be treated, early recognition of these disorders is important.

Search Strategy and Selection Criteria

We reviewed articles regarding ocular motility disorders and IEM up to June 2017. References were identified by PubMed, text book search, and through citations in relevant articles and books. Only articles published in English were included. Search terms are in Supplementary Appendix I. Only IEMs with at least 2 patients with some type of eye movement disorder were included in the review. Although we focused on late-onset IEM (adolescent-onset 16-18 years of age, adult-onset > 18 years of age), it is difficult to discriminate specifically between early- and late-onset forms, given that eye movement disorders are frequently not described in the literature. For that reason, children were also included in this review. We included mitochondrial diseases as a combined disease group instead of specific subtypes. We excluded articles in which nystagmus secondary to blindness was the only ocular motor finding. Supplementary Appendix II presents a list of references with videos of eye movement disorders in IEM.

Examination of Eye Movements

Disorders of eye movement can be categorized as peripheral and central (Table 1). Peripheral eye movement disorders are particularly frequent in mitochondrial disorders and commonly affect the two eyes differently, resulting in ocular misalignment and diplopia. Progressive external ophthalmoplegia (PEO) is an important exception to this rule. Because of the insidious onset and slow progression, patients do not complain of diplopia and may be unaware of any disorder of eye movements. Central causes of ocular motor abnormalities usually affect both eyes.

Clinical examination of the eye movements in all patients with a suspected IEM is essential. Patients themselves may not report visual symptoms or may only have nonspecific complaints. Table 2 provides a short step-by-step overview of the clinical examination of eye movements. Every step in the table needs to be followed because different types of eye movement disorders can exist in 1 patient.

Video-oculography (VOG) allows for better quantitative documentation of abnormalities. Typically, a digital camera mounted in goggles uses the contrast between the pupil and iris to track the movement and position of one or both of the eyes.
VOG is an effective user- and patient-friendly tool to quantify eye movements, including subtle changes in latency, velocity, and accuracy of saccades. It can be used to support or make a diagnosis and measure effectiveness of treatment during follow-up. For example, in Niemann-Pick type C (NP-C), saccadic parameters measured by VOG have been reported to be a robust indicator of efficacy of treatment with Miglustat.

**Inborn Errors of Metabolism Associated With Ocular Motor Disorders**

We will discuss abnormalities of eye movements in IEM. An overview of the various IEMs associated with ocular motor disorders, including the underlying gene defect, metabolic abnormalities, age of onset, early-
onset symptoms, and treatment, is given in Table 3. Table 4 presents the described eye movement disorders for each of those IEMs.

**Lysosomal Storage Diseases**

Late-onset NP-C usually presents with neurological problems. Movement disorders are frequent, particularly in these adolescent- and adult-onset forms. Eye movement disorders are also an important feature. Vertical supranuclear gaze palsy (VSGP) is a key feature and is present in approximately 65% of patients. VSGP in patients with NP-C is characterized by a paralysis of vertical (especially downward) saccades, whereas smooth pursuit is initially spared. Horizontal saccades are initially preserved, but are ultimately affected as the disease progresses. A so-called round-the-houses phenomenon occurs when attempting vertical saccades: The eyes do not move directly up and down, but in a lateral arc (Video 1). A similar phenomenon occurs during horizontal saccades in Gaucher’s disease. No abnormalities of vestibulo-ocular responses have been found. Treatment is possible with Miglustat. Gaucher’s disease type 2 (acute neurological form) and type 3 (subacute neurological form) are the neuropathic forms of this lysosomal storage disorder. Gaucher’s disease type 2 presents during infancy and abnormalities of eye movements are early signs in affected children, including ocular motor paralysis, slowness of saccades, oculomotor “apraxia,” and strabismus. Gaucher’s disease type 3 presents during childhood or adolescence. Movement disorders are common in type 3, particularly ataxia and parkinsonism. However, patients often present with (myoclonus) epilepsy and supranuclear gaze palsy that only affects horizontal gaze. Horizontal saccades are markedly slow and may show a curved trajectory, whereas vertical saccades are initially preserved. Vestibulo-ocular responses may be impaired. Ocular motor apraxia, which in fact reflects abnormal patterns of head motion associated with defects in initiation of saccades, is also observed in Gaucher’s types 2 and 3. Similar to NP-C, patterns of abnormal saccades can be used to monitor progression of disease. Gaucher’s disease type 1 is the chronic non-neurological form; however, subtle slowness of saccades has been reported in some patients. Enzyme replacement therapy and substrate reduction therapy are available. In the late-onset form of Tay-Sachs disease (GM2 gangliosidosis), motor symptoms are frequent. These are caused by motor neuron dysfunction and cerebellar involvement with ataxia. Abnormalities of eye movements are not a classic feature of late-onset Tay-Sachs disease, but impaired smooth pursuit with square-wave jerks (saccadic intrusions), transient decelerations of saccades, and up-gaze palsy have been described. Vestibulo-ocular responses are normal. In early-onset Tach-Sachs disease, vertical gaze is impaired early and horizontal gaze later in the disease. Treatment is not available.

The clinical picture of Sandhoff’s disease (GM2 gangliosidosis) is similar to Tay-Sachs disease. Early childhood forms are most common. Late-onset forms of Sandhoff’s disease are rare and have a milder phenotype. They often present as a complex neurological disorder with ataxia, chorea, tremor, dystonia, or parkinsonism in combination with motor neuron dysfunction. Abnormalities of eye movements include impaired horizontal and vertical saccades with nystagmus. A patient with adult-onset Sandhoff’s disease and pendular nystagmus in combination with palatal tremor has been described. Treatment is not available.

**Disorders of Lipid Metabolism**

Signs of abetalipoproteinemia occur early in life and progress with time. Neurological manifestations resulting from vitamin deficiency often begin in the first or second decade of life. Low vitamin E in particular can cause progressive neurological symptoms affecting the peripheral and central nervous system. Adult patients show malabsorption, steatosis, abnormal liver transaminases, and neurological signs. Abnormalities of eye movements are typical, including progressive gaze disturbances attributed to paresis of the medial rectus muscles and a characteristic pattern of dissociated nystagmus. The latter consists of an intense nystagmus, but with limited range in the adducting eye, and a less-intense nystagmus, but with full range, in the abducting eye. Patients complain of trouble reading and of difficulties associated with impaired convergence. Saccades are slow and hypometric. Vestibular nystagmus and optokinetic nystagmus have abnormal or absent quick phases. A low-fat diet with reduced long-chain fatty acids and fat-soluble vitamin supplements is recommended.

Late-onset cerebrotendinous xanthomatosis is characterized by tendon xanthomas, psychiatric symptoms, and neurological symptoms, including pyramidal, cerebellar, and extrapyramidal signs in the second or third decade of life. Patients show abnormal pursuit, increased saccadic intrusions, multitrap saccades, and antisaccade deficits. Chenodeoxycholic acid and statin therapy are an effective treatment and can prevent neurological involvement if started early.

**Disorders of Carbohydrate Metabolism**

Symptoms of glucose transporter type 1 deficiency usually occur early in life, but may present in adolescence or adulthood. In the late presentation form, paroxysmal exercise-induced dyskinesia occurs that...
| TABLE 3. Inborn errors of metabolism associated with eye movement abnormalities |
|---------------------------------------------------------------|
| **Gene** | **Inheritance** | **Functional Consequences** | **Age of Onset** | **Early-Onset Symptoms** | **Treatment** |
|----------|----------------|----------------------------|------------------|--------------------------|--------------|
| Lysosomal storage diseases | | | | | |
| Niemann-Pick C1, NP-C2 | AR | Lipid accumulation in cells | Early infantile-adulthood | Hepatosplenomegaly, neuropsychiatric symptoms later in life | Miglustat |
| Gaucher's disease | GBA | Accumulation of glucosylceramide and the cytotoxic derivative of glucosylceramide | Early infantile-adulthood | Type 1: hepatosplenomegaly, bone anomalies, cytopenia Type 2: early death attributed to neurological symptoms Type 3: progressive encephalopathy and systemic symptoms | Miglustat, enzyme replacement therapy |
| Tay-Sachs disease | HEXA | Disturbance of catabolism and eventually accumulation of GM2 ganglioside, particularly in neurons | Usually infantile, sometimes late-onset | Early death attributed to psychomotor retardation, neurodegeneration, and muscle weakness Cherry-red spot in the ocular fundus | |
| Sandhoff's disease | HEXB | Disturbance of catabolism and eventually accumulation of GM2 ganglioside, particularly in neurons | Usually infantile, sometimes late-onset | Early death attributed to psychomotor retardation, neurodegeneration, and muscle weakness Cherry-red spot in the ocular fundus | |
| Disorders of lipid metabolism | | | | | |
| Abetalipoproteinemia | MTTP | Impairment of the absorption of dietary fats, cholesterol, and fat-soluble vitamins | Childhood, sometimes late-onset | Failure to thrive and growth failure, hepatomegaly with stratosis, diarrhea, ataxia | High-dose vitamin E, supplementation of vitamin A,D, and K, low-fat diet, Chenodeoxycholic acid and statin therapy |
| Cerebrotendinous xanthomatosis | CYP27A1 | Cholesterol and cholesterol accumulation in cells | Childhood-adulthood | Diarrhea, jaundice, premature cataracts, ataxia; xanthomata in the second or third decade | |
| Disorders of carbohydrate metabolism | | | | | |
| Glucose transporter type 1 deficiency | SLC2A1 | Impairment of the transport of glucose from the blood to cerebral tissue | Infantile-childhood, sometimes late-onset | Psychomotor retardation, seizures, microcephaly, spasticity, movement disorders | Ketogenic diet |
| Disorders of mineral, metal, and vitamin metabolism | | | | | |
| Wilson's disease | ATP7B | Accumulation of copper, particularly in the liver and brain | Early childhood-adulthood | Liver disease, neurological and psychiatric symptoms, Kayser-Fleischer ring | Penicillamine, trientine, zinc |
| Hypermanganesemia with dystonia 1 | SLC30A10 | Accumulation of manganese in liver and basal ganglia | Childhood-adolescence | Severe dystonia and other movement disorders, liver dysfunction | Chelation therapy, iron supplementation |
| Panthenate kinase-associated neurodegeneration | PKAN2 | Accumulation of iron, especially in the globus pallidus | Childhood-adolescence | Dystonia, chorea, rigidity, dysarthria, pigmentary retinopathy, developmental delay | |
| Adult-onset dystonia-parkinsonism | PLA2G6 | Accumulation of iron, especially in the globus pallidus | Adulthood | Parkinsonism, dystonia, cognitive decline | |
| Disorder                                                                 | Gene(s)       | Inheritance | Symptoms                                                                 | Treatment/Prevention                                                                 |
|------------------------------------------------------------------------|---------------|-------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Biotin-thiamine-responsive basal ganglia disease                        | SLC19A3       | AR          | Impairment of thiamine uptake into cells, causing destruction of the head of the caudate and putamen | Infantile-adolescence, Acute dystonia, encephalopathy                                |
| Ataxia with vitamin E deficiency                                        | TTPA          | AR          | Impairment of incorporation of vitamin E into very-low-density lipoprotein, leading to low plasma levels of vitamin E | Childhood-adulthood, Ataxia, areflexia, impaired proprioception                      |
| Disorders of amino acid metabolism                                      |               |             |                                                                           | Vitamin E                                                                            |
| Maple syrup urine disease                                               | BCKDHA, BCKDHB, DBT | AR          | Preventing the normal breakdown of leucine, isoleucine, and valine, leading to accumulation of these amino acids | Infantile, late-onset presentation is rare, Maple syrup odor in the cerumen and later in urine, poor feeding, progressive encephalopathy, intermittent apnea, stereotyped movements |
| Glutaric aciduria type 1                                                | GCDH          | AR          | Preventing the breakdown of lysine, hydroxylysine, and tryptophan, leading to accumulation of metabolites | Childhood-adulthood, Acute encephalopathic crises, dystonia (with insidious onset) |
| Disorders of purine or pyrimidine metabolism                            |               |             |                                                                           | Low-protein diet, leucine-, isoleucine-, and valine-free amino acid supplement, emergency regimens |
| Lesch-Nyhan syndrome                                                   | HPRT          | X-linked recessive | Affecting the breakdown of purines, leading to high levels of uric acid in blood | Childhood, sometimes late-onset, Developmental delay, hypotonia, ataxia, retinitis pigmentosa, strabismus, seizures, abnormal fat distribution |
| Peroxisomal disorders                                                   | PEX genes     | AR          | Affecting the formation of functional peroxisomes                        | Infantile, sometimes late-onset, Severe dystonia and behavioral abnormalities, including self-injury |
| Neuronal circuit disorders                                              |               |             |                                                                           | Treatment of hyperuricemia                                                          |
| Neurotransmitter disorders                                              |               |             |                                                                           |                                                                                     |
| Aromatic L-amino acid decarboxylase deficiency                         | DDC           | AR          | Reduced production of dopamine, serotonin, and tryptophine               | Usually infantile, sometimes late-onset, Dystonia, psychomotor retardation, spasticity, autonomic dysfunction |
| Tyrosine hydroxylase deficiency                                         | TH            | AR          | Impairment of the conversion of L-tyrosine to L-dopa                      | Usually infantile, sometimes late-onset, Dystonia, mild intellectual deficit, L-dopa |
| GTP-C4-I deficiency                                                    | GCH1          | AR or AD    | Impairment of the tetrahydrobiopterin (BH4) biosynthesis                 | Infantile-adolescence, Psychomotor retardation, convulsions, drowsiness, abnormal movements, autonomic dysfunction, L-dopa, 5-hydroxytryptophan, and tetrahydrobiopterin (the latter two only in recessive forms) |
| Sepiapterin reductase deficiency                                        | SPR           | AR (or AD?) | Impairment of the tetrahydrobiopterin (BH4) biosynthesis                | Usually infantile, Dystonia, psychomotor retardation, axial hypotonia, weakness, L-dopa, 5-hydroxytryptophan, and tetrahydrobiopterin |

(Continues)
predominantly manifests as dystonia, chorea, and ballism. Epilepsy is also observed. Abnormalities of eye movements are common and may be highly characteristic brief multidirectional paroxysmal episodes of rapid eye movements in combination with head movements in the same direction, a phenomenon called aberant gaze saccades. Eye rolling and fluttering, strabismus, opsoclonus, and limitation of vertical eye movements have also been described. Early diagnosis is important because this disorder can be treated with a ketogenic diet.

### Disorders of Mineral, Metal, or Vitamin Metabolism

Symptoms of Wilson’s disease often begin in the teenage years. Liver disease is frequently the presenting sign, but psychiatric and neurological symptoms including movement disorders are also frequent presentations. The Kayser-Fleischer ring, copper deposits that form a ring in the cornea, is the ophthalmological hallmark of Wilson’s disease. Abnormalities of eye movements are frequently present. Impaired vertical, but sometimes also horizontal pursuit, selective slowing of downward saccades, and dysmetria of saccades are all reported. Gaze distractibility has also been described in which patients cannot fix their eyes on a stationary or moving object for more than a few seconds without being distracted by other stimuli. At least 1 patient with oculo-gyric crises has been reported on. Treatment is possible with chelation therapy.

Adult-onset hypermanganesemia with dystonia 1 is characterized by parkinsonism, whereas children usually present with dystonia. Bilateral hyperintensities in the basal ganglia and white matter attributed to accumulation of manganese are typically observed on brain imaging. Increased latency of saccades, misdirected antisaccades, and multistep saccades have been observed by one of the authors (A.R., personal observations). Chelation therapy and iron supplementation are recommended.

Pantothenate kinase-associated neurodegeneration (or NBIA type 1) is the most common form of neurodegeneration with brain iron accumulation (NBIA). This is reflected in the “eye-of-the-tiger” sign on brain MRI. Late-onset disease occurs during the second or third decade. It is slowly progressive and is characterized by speech problems, movement disorders, and psychiatric symptoms. Horizontal and vertical supranuclear gaze palsy, impaired saccades, abnormal optokinetic nystagmus, and impaired horizontal vestibulo-ocular responses have been described. Oculogyric crisis has been reported in 1 patient. Treatment with chelation therapy is not effective.

Adult-onset dystonia-parkinsonism (NBIA type 2) also belongs to the heterogeneous group of degenerative...
### TABLE 4. Abnormalities of eye movements in inborn errors of metabolism

| Lysosomal storage diseases | Disorders of lipid metabolism | Disorders of carbohydrate metabolism | Disorders of mineral, metal, and vitamin metabolism | Disorders of amino acid metabolism | Congenital disorders of glycosylation | Disorders of purine or pyrimidine metabolism | Peroxisomal disorders | Neurotransmitter disorders | Energy metabolism disorders |
|----------------------------|--------------------------------|--------------------------------------|-----------------------------------------------|----------------------------------|--------------------------------------|----------------------------------|-------------------|----------------------------|----------------------------|
| Niemann-Pick type C | x(V) | x | x | x | x | + |  |  |  |
| Gaucher's disease type 1 | x | x | x | x | x | + |  |  |  |
| Gaucher's disease type 2 | x | x | x | x | x | + |  |  |  |
| Gaucher's disease type 3 | x | x | x | x | x | + |  |  |  |
| Tay-Sachs disease, infantile form | x | x | x | x | x | + |  |  |  |
| Tay-Sachs disease, late-onset form | x | x | x | x | x | + |  |  |  |
| Sandhoff's disease | x | x | x | x | x | + |  |  |  |
| Abetalipoproteinemia | x | x | x | x | x | + |  |  |  |
| Cerebrotendinous xanthomatosis | x | x | x | x | x | + |  |  |  |
| Disorders of amino acid metabolism | Maple syrup urine disease | x | x | x | x | x | x | + |  |
| Glutaric aciduria type 1 | x | x | x | x | x | x | x | x | x |
| Congenital disorders of glycosylation | Phosphomannomutase 2 deficiency | x | x | x | x | x | x | x | x |
| Disorders of purine or pyrimidine metabolism | Lesch-Nyhan syndrome | x | x | x | x | x | x | x | x |
| Peroxisomal disorders | Zellweger spectrum disorders | x | x | x | x | x | x | x | x |
| Neurotransmitter disorders | Dopamine transporter deficiency syndrome | x | x | x | x | x | x | x | x |
| Other disorders of dopamine synthesis or transport | x | x | x | x | x | x | x | x | x |
| Energy metabolism disorders | Mitochondrial diseases | x | x | x | x(P(EO)) | x | x | x | x | x |
| Pyruvate dehydrogenase E2 deficiency | x | x | x | x(V) | x | x | x | x | x |

x: Present.  
+/-: Inconstant.  
+/-: Present.  
?: Unknown.  
H: Primarily horizontal.  
V: Primarily vertical.  
(P(EO)): Progressive external ophthalmoplegia.
disorders causing iron accumulation. Adults usually present before the age of 30 and have parkinsonism, dystonia and cognitive decline. Ophthalmic features include strabismus, up-gaze palsy, impaired pursuit with saccadic intrusions, and pendular nystagmus. Vestibulo-ocular responses are not impaired.

A case of oculogyric crisis induced by levodopa has been described in a patient with adult-onset dystonia-parkinsonism. Only symptomatic treatment is available.

Emergency treatment is necessary during metabolic episodes and intercurrent illnesses. In addition to acute dystonia and encephalopathy, bilateral external ophthalmoplegia is observed. Diagnosis is important because treatment with thiamine and biotin can be life-saving.

Finally, onset of ataxia with vitamin E deficiency can be at any age. Symptoms include ataxia, areflexia, and impaired proprioception. Nystagmus is observed as part of a cerebellar syndrome. Impaired smooth pursuit, slow saccades, ocular motor apraxia, and strabismus have been reported. Treatment is with high-dose vitamin E supplementation.

Disorders of Amino Acid Metabolism

Four clinical subtypes of maple syrup urine disease (MSUD) are described. Classic MSUD presents soon after birth and is a severe and often rapidly lethal disorder. The phenotypes of the other subtypes (intermediate, intermittent, and thiamine-responsive MSUD) are overlapping. Presentation in adulthood is very rare. Patients with MSUD may decompensate during catabolic states and develop behavioral changes, nausea, vomiting, and eventually coma attributed to cerebral edema. Movement disorders may also be present. Abnormalities of eye movements are described in infants and vary from up-gaze palsy and adduction weakness to absence of voluntary eye movements with absent vestibulo-ocular reflexes. Treatment is with a low-protein diet in combination with a leucine-, isoleucine-, and valine-free amino acid supplement. Emergency treatment is necessary during metabolic stress, such as intercurrent illnesses.

Glutaric aciduria type 1 (GA1) usually begins in childhood, but adult-onset has been reported as well. Catabolic episodes and intercurrent illnesses result in damage to the caudate nucleus and putamen, causing severe dystonia. Ocular abnormalities include intraretinal haemorrhages, cataract, and pigmentary retinopathy. A 19-year-old woman with GA1 showed horizontal nystagmus, upward gaze palsy, and paralysis of convergence. Other patients with gaze palsy have been described, but gaze palsy in these patients might be secondary to increased intracranial pressure attributed to the intracranial haemorrhages that may be present in GA1.

Dietary treatment with a low-lysine diet and carnitine supplementation prevents damage to the striatum. Similar to MSUD, emergency treatment is necessary to prevent catabolism during periods of fever or prolonged fasting.

Congenital Disorders of Glycosylation

Phosphomannomutase 2 deficiency (PMM2-CDG or CDG1A) is the most common congenital disorder of glycosylation. The phenotype is variable, and multiple organs can be involved. PMM2-CDG is usually diagnosed in childhood, but attenuated forms present later. In adulthood, the symptoms may be mild and include ataxia and learning difficulties. A whole range of ocular manifestations can occur and include strabismus, impaired smooth pursuit, nystagmus, ocular flutter, ocular motor apraxia, impaired optokinetic nystagmus, and impaired vestibulo-ocular reflexes. Strabismus and nystagmus might be secondary to visual impairment, although they are also described in patients with PMM2-CDG who have normal vision. Other subtypes of congenital disorders of glycosylation 1 are less common, but some of these patients also show strabismus and nystagmus. With the exception of a few subtypes of CDG syndromes, treatment is not available.

Disorders of Purine or Pyrimidine Metabolism

Variants of Lesch Nyhan syndrome are described that present in early adulthood with symptoms of hyperuricemia, for example, nephrolithiasis, crystalluria, and gout. Ocular motor abnormalities are observed particularly in severe (early-onset) HPRT deficiency and include impaired smooth pursuit and difficulty initiating voluntary saccades that appears as an ocular motor apraxia. Hyperuricemia must be treated.

Neurotransmitter disorders

Disorders of neurotransmitters, especially those that affect the dopaminergic pathways, can cause dystonia with
oculogyric crises. Response to low doses of l-dopa in some of these diseases is excellent. Neurotransmitter disorders can be divided into those affecting synthesis, those affecting dopamine transport, and those affecting degradation.

Oculogyric crisis is frequently observed in disorders affecting dopamine synthesis, whereas other abnormalities of eye movements are rare in these disorders.\(^{87}\) Many of these disorders present early in life and, for most of the neurotransmitter disorders, late-onset presentation is rare. Patients with milder forms of these disorders may remain undiagnosed until adolescence or adulthood, or may be mistakenly diagnosed with cerebral palsy.\(^{21}\) However, recognition of these disorders is important because patients can improve dramatically when treated properly. Most of the late-onset neurotransmitter disorders are caused by autosomal dominant GTP-CH-I deficiency. Patients present with dystonia of the lower limbs that usually progresses to generalized dystonia, although the late-onset form can also be associated with parkinsonism.\(^{88}\) Autosomal recessive forms of GTP-CH-I deficiency have also been described. Oculogyric crises are more frequent in recessive than dominant forms of GTP-CH-I deficiency.\(^{89-91}\) Patients with aromatic L-amino acid decarboxylase deficiency (AADC),\(^{21,92}\) tyrosine hydroxylase deficiency,\(^{93-96}\) and 6-pyruvoyl-tetrahydropterin synthase deficiency\(^{97,98}\) may show oculogyric crisis, in particular in AADC in which oculogyric crisis is one of the key features.\(^{92,99,100}\)

Finally, oculogyric crisis is also described in sepiapterin reductase deficiency.\(^{101-103}\)

Disorders affecting dopamine transport include brain dopamine-serotonin vesicular disease (vesicular monoamine transporter 2 deficiency) and dopamine transporter deficiency syndrome (DAT deficiency). In the latter, adult onset is reported with parkinsonism and psychiatric symptoms.\(^{104}\) Both disorders are associated with oculogyric crisis.\(^{87,105,106}\) Other abnormalities of eye movements are also observed in DAT deficiency, including saccadic intrusions during smooth pursuit, saccadic oscillations (ocular flutter), slow saccadic eye movements, and ocular motor apraxia.\(^{87,104,107}\)

Energy Metabolism Disorders

Mitochondrial diseases are a group of disorders caused by mutations in mitochondrial DNA (mtDNA; either maternally inherited or de novo) or nuclear DNA (Mendelian inherited). Tissues with high energy needs are commonly affected, including brain, heart, and skeletal muscles. There is a wide range of clinical phenotypes, and onset varies widely. Neurological involvement causes movement disorders, psychomotor retardation or regression, epilepsy, muscle weakness, and migraine.\(^{108}\) Adult onset of mitochondrial disease is especially frequent in disorders caused by multiple deletions in mtDNA, probably attributed to accumulation of mtDNA defects.\(^{108}\)

Conclusions

We have reviewed IEM in which the onset of symptoms can occur relatively late in life and in which ocular motor abnormalities can be a prominent sign. Recognition of these patterns of abnormalities of eye movements is important because they may be the key to accurate early diagnosis and thus to a timely start of treatment. Unfortunately, there continues to be a lack of information about eye movement disorders in many IEMs because little attention is given to them in daily
practice. Examination of the vestibular system, in particular, is neglected in most studies even though it often provides essential information about localization and diagnosis. Disorders of hearing are commonly recognized in many IEMs, but vestibular function is rarely commented upon. A standard, focused examination of the different subtypes of eye movements (range of motion, gaze-holding, saccades, pursuit, and vestibular responses) can be performed relatively quickly in most patients during routine physical examination. Testing with video-oculography has also become more user- and patient-friendly and helps to quantify the eye movement abnormalities, making these abnormalities a valuable biomarker for following the natural course of disease or the response to therapies.

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Supporting Data

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