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Koens, Lisette H; Tuitert, Inge; Blokzijl, Hans; Engelen, Marc; Klouwer, Femke C C; Lange, Fiete; Leen, Wilhelmina G; Lunsing, Roelineke J; Koelman, Johannes H T M; Verrips, Aad

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Eye movement disorders in inborn errors of metabolism: A quantitative analysis of 37 patients

Lisette H. Koens[1,2] | **Inge Tuitert**[1,2] | **Hans Blokzijl**[3] | **Marc Engelen**[4] | **Femke C. C. Klouwer**[4] | **Fiete Lange**[1] | **Wilhelmina G. Leen**[5] | **Roelineke J. Lunsing**[1] | **Johannes H. T. M. Koelman**[4] | **Aad Verrips**[5] | **Tom J. de Koning**[2,6,7] | **Marina A. J. Tijssen**[1,2]

[1]Department of Neurology and Clinical Neurophysiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[2]Expertise Center Movement Disorders Groningen, University Medical Center Groningen (UMCG), Groningen, The Netherlands

[3]Department of Gastroenterology and Hepatology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[4]Department of Neurology and Clinical Neurophysiology, University of Amsterdam, Amsterdam University Medical Center, Amsterdam, The Netherlands

[5]Department of Neurology and Clinical Neurophysiology, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands

[6]Department of Genetics, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[7]Department of Pediatrics, Clinical Sciences, Lund University, Lund, Sweden

Correspondence
Marina A. J. Tijssen, Department of Neurology, University Medical Center Groningen, Hanzeplein 1, 9700 RB Groningen, The Netherlands.
Email: m.a.j.de.koning-tijssen@umcg.nl

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Abstract

Inborn errors of metabolism are genetic disorders that need to be recognized as early as possible because treatment may be available. In late-onset forms, core symptoms are movement disorders, psychiatric symptoms, and cognitive impairment. Eye movement disorders are considered to be frequent too, although specific knowledge is lacking. We describe and analyze eye movements in patients with an inborn error of metabolism, and see whether they can serve as an additional clue in the diagnosis of particularly late-onset inborn errors of metabolism. Demographics, disease characteristics, and treatment data were collected. All patients underwent a standardized videotaped neurological examination and a video-oculography. Videos are included. We included 37 patients with 15 different inborn errors of metabolism, including 18 patients with a late-onset form. With the exception of vertical supranuclear gaze palsy in Niemann-Pick type C and external ophthalmolplegia in Kearns-Sayre syndrome, no relation was found between the type of eye movement disorder and the underlying metabolic disorder. Movement disorders were present

Eye movement disorders in inborn errors of metabolism are very heterogeneous, even in patients with the same disorder, with the exception of a vertical supranuclear gaze palsy in Niemann-Pick type C and a progressive external ophthalmoplegia in Kearns-Sayre syndrome.

in 29 patients (78%), psychiatric symptoms in 14 (38%), and cognitive deficits in 26 patients (70%). In 87% of the patients with late-onset disease, eye movement disorders were combined with one or more of these core symptoms. To conclude, eye movement disorders are present in different types of inborn errors of metabolism, but are often not specific to the underlying disorder. However, the combination of eye movement disorders with movement disorders, psychiatric symptoms, or cognitive deficits can serve as a diagnostic clue for an underlying late-onset inborn error of metabolism.

KEYWORDS

eye movement disorders, inborn errors of metabolism, late-onset, movement disorders

1 | INTRODUCTION

The introduction of next-generation sequencing has led to unexpected diagnoses, including inborn errors of metabolism (IEMs).[1,2] IEMs are genetic disorders that cause impairment of a biochemical pathway, for example, dysfunction of an enzyme or transporter involved in cellular metabolism.[3] Age of onset is often in childhood, but late-onset forms presenting in adolescence or adulthood are more recognized since the implementation of next-generation sequencing. So, the challenge for the clinician is to recognize patients that might suffer from an underlying IEM to perform timely diagnostics and diminish diagnostic delay because treatment is available for some IEMs.

Identification of patients with an IEM can be challenging as symptoms are often heterogeneous, and patients with late-onset forms can present with different phenotypes than children with the classical young-onset forms. In the late-onset forms, movement disorders, psychiatric symptoms, and cognitive deficits are often the presenting symptoms.[4–6] Interestingly, abnormal eye movements appear to be a frequent symptom as well, but are frequently missed as physicians do not always look for them, and patients may only complain about nonspecific symptoms, such as vertigo, imbalance, and frequent falling.[7,8]

Recognition of eye movement disorders in patients is important because they may serve as an additional clue in the diagnosis of an IEM. In the literature, specific patterns of ocular motor disorders are described and linked to specific types of IEMs. This is for example the case in patients with Niemann-Pick type C (NP-C), where a vertical supranuclear gaze palsy (VSGP) is an important characteristic of the disease.[9,10] In many other IEMs, eye movement disorders are not extensively investigated and described, although they might be present early in the disease course.[8]

In the current prospective study, we systematically analyzed eye movement disorders in adolescent and adult patients with an IEM to determine eye movement characteristics and to assess whether they can serve as an extra clue to the diagnosis of IEMs.

2 | METHODS

Patients from the University Medical Center Groningen, Amsterdam University Medical Center, and Canisius Wilhelmina Hospital were included from November 2015–January 2020. This study was approved by the medical ethical committee of the University Medical Center Groningen (METc2016/616). All subjects and/or parents gave written informed consent.

Demographics, disease characteristics, and treatment data were collected from patient files and anamnesis. All patients underwent a standardized videotaped neurological examination. The following movement disorders were scored through consensus-based discussion: ataxia, dystonia, myoclonus, chorea, parkinsonism, tremor, and tics. Additional non-neurological and neurological abnormalities, such as spasticity, were documented as well. Video-oculography (VOG) was performed in all patients to evaluate eye movements during rest (with and without fixation), gaze, smooth pursuit, (self-initiated) saccades, optokinetic nystagmus, and eye movements during hyperventilation (see the Supplementary Information I and II for the protocol, definitions of eye movement abnormalities, and norm data). An adolescent- or adult-onset was defined as age of onset ≥12 years.

Inclusion criteria were age at examination ≥12 years, a confirmed IEM (biochemical and/or genetically), and eye movement abnormalities during neurological examination. Exclusion criteria were severe visual disturbances, severe ptosis, or severe cognitive disturbances that would interfere with the VOG (see Supplementary

Information I, Table S2 for information about selection of patients).

Statistical analyses were performed using IBM SPSS Statistics for Windows (version 23). To examine differences in eye movement disorders related to the presence of other variables (movement disorders, type of movement disorder, psychiatric symptoms, cognitive impairment, and different types of IEMs) separate Pearson chi-square tests were performed (e.g., the presence of a VSGP in NP-C). The Bonferroni correction was used because of the number of statistical tests, and the alpha was set at 0.001.

3 | RESULTS

We included 37 patients with 15 different IEMs, including 18 patients with an adolescent- or adult-onset. The median age was 34 years (range 12–67), median age of diagnosis was 23 years (range 0–61) with a median diagnostic delay of 5 years (range 0–45). The patient characteristics are shown in Table 1.

3.1 | Eye movement disorders

During the first documented neurological examination, eye movement abnormalities were reported in 14 patients, while in 11 patients eye movements were normal. In 10 patients, eye movements were not examined or reported at that moment. In the remaining patients, no neurological examination was performed prior to this study. Eye movement abnormalities were noticed by the patient self or their relatives in 11 patients.

Figure 1 presents an overview of the different eye movement abnormalities detected by VOG. Saccadic oscillations and impaired smooth pursuit were most frequently observed, followed by a VSGP. Hyperventilation-induced eye movement abnormalities were examined in 34 patients, and abnormalities were found in eight of them, including four patients with cerebrotendinous xanthomatosis, two with Wilson's disease, one with ataxia with vitamin E deficiency, and one with GLUT-1 deficiency. None of the included patients had a history of oculogyric crisis or showed ocular motor apraxia.

Figure 2 presents an overview of the impaired modalities of eye movements in relation to the underlying IEM. Although most of the observed eye movement disorders were not associated with a type or group of IEMs, there were two exceptions to this. First, a VSGP was strongly related to NP-C, χ^2 (1) = 23.69, $p < 0.001$. All 10 included patients with NP-C showed a VSGP during testing saccades, combined with abnormal horizontal saccades in seven patients. Horizontal optokinetic nystagmus (OKN) was impaired in four patients, vertical OKN in all of them. A so-called "round-the-houses" phenomenon, where the eyes move in a lateral arc when attempting to look up and down, was found in four NP-C patients, and is illustrated in Video S1. In the other patients, vertical saccades were too severely affected for assessment of this. Second, progressive external ophthalmoplegia was only present in the mitochondrial disease *Kearns-Sayre syndrome*, χ^2 (1) = 35.00, $p < 0.001$. This patient showed a progressive external ophthalmolplegia consisting of a ptosis, impaired abduction and adduction (more severe in the right eye), and impaired upgaze. Downgaze was not assessable due to the ptosis (see Video S2).

No clear relation was found between eye movement disorders and other IEMs (Figure 2). In most included disorders, the ocular motor abnormalities were heterogeneous (Table 2).

The other three patients with different *mitochondrial diseases* included one patient with a *LIG-3* mutation, and two patients with a mitochondrial trifunctional protein deficiency (MTP-deficiency). The patient with the *LIG-3* mutation had among others a history of macular degeneration and ischemic stroke, leading to a left-sided neglect. In this patient, saccadic oscillations in alternating directions and downward drift were found during rest, with saccadic intrusions during smooth pursuit. OKN to the right was impaired. One of the patients with the MTP-deficiency showed microsaccadic oscillations during rest, both had dysmetric saccades and impaired OKN in vertical direction. Ophthalmoplegia was not present in these three patients.

All four patients with *cerebrotendinous xanthomatosis* (CTX) had a history of cataract and showed pupil abnormalities. In two patients, microsaccadic oscillations were observed during rest, which also interfered with smooth pursuit. In one patient, shown in Video S3, there were random horizontal and vertical eye movements that seemed to be associated with blinking, which aggravated during hyperventilation. This patient also showed nystagmus during self-initiated saccades. In two other patients, saccades showed impaired precision (combined hypo- and hypermetric). Horizontal microsaccadic oscillations were present during hyperventilation in two patients, which can be seen in Video S4. In one of these patients, the microsaccadic oscillations were not present during rest.

Two patients with *glucose transporter type 1 deficiency* (GLUT-1 deficiency) were included. Upbeat nystagmus was observed during rest in one of them, while the other showed saccadic oscillations that increased during hyperventilation. Smooth pursuit was impaired in both patients with microsaccadic intrusions and abnormal

TABLE 1 Patient characteristics

Diagnosis	Sex	Age (years)	Mutation	Gene	Age of onset (years)	Diagnostic delay (years)	First symptoms	Movement disorders	Psychiatric history	Cognitive impairment	Eye movement abnormalities	
											Described by patient and/or family	Described at first visit neurologist
Lysosomal storage disorders												
Niemann-Pick type C	F	35	Compound heterozygous mutations c.1211G>A (p. Arg404Gln) and c.2861C>T (p. Ser954Leu)	NPC-1	18	5	Cognitive failure, VSGP, psychosis	+	+	+	+	+
Niemann-Pick type C	F	25	Homozygous mutations c.3182T>C (p.IIe1061Thr)	NPC-1	8	13	Cognitive failure, myoclonus	+	−	+	−	−
Niemann-Pick type C	M	61	Compound heterozygous mutations c.2474A>G (p.Tyr825Cys) and c.3019C>G (p.Pro1007Ala)	NPC-1	52	7	Myoclonus	+	−	+	−	Not examined
Niemann-Pick type C	F	20	Homozygous mutations c.1918G>A (p.Gly640Arg)	NPC-1	14	4	Myoclonus, VSGP	+	−	+	+	+
Niemann-Pick type C	M	19	Compound heterozygous mutations c.346C>T (p.R116X) and c.247A>G	NPC-1	14	3	Psychosis, dystonia, VSGP	+	+	+	+	+
Niemann-Pick type C	M	19	Compound heterozygous mutations c.1918G>A (p.Gly640Arg) and c.3451G>A (p.Ala1151Thr)	NPC-1	3	11	Ataxia	+	−	+	+	−
Niemann-Pick type C	F	62	Homozygous mutations c.2861C>T, p.(Ser954Leu)	NPC-1	30	31	Ataxia and dysarthria	+	−	+	−	−
Niemann-Pick type C	M	58	Only one mutation found c.180G>T p.(Gln60His)	NP-C1	53	5	Depression, personality change, fatigue	+	+	+	−	+
Niemann-Pick type C	M	36	Compound heterozygous mutations c.2861C>T, p.(Ser954Leu) and c.1574A>T, p.(Asp525Val)	NPC-1	16	20	Dysarthria, ataxia, spasticity	+	−	+	+	Not examined

TABLE 1 (Continued)

Diagnosis	Sex	Age (years)	Mutation	Gene	Age of onset (years)	Diagnostic delay (years)	First symptoms	Movement disorders	Psychiatric history	Cognitive impairment	Eye movement abnormalities	
											Described by patient and/or family	Described at first visit neurologist
Niemann-Pick type C	F	34	Compound heterozygous mutations c.2861C>T, p.(Ser954Leu) and c.1574A>T, p.(Asp525Val)	NPC-1	31	3	Dysarthria, myoclonus	+	−	−	−	NA[a]
Metachromatic leukodystrophy	M	16	Compound heterozygous mutations c.245C>T (p.Pro82leu) and c.1144G>A (p.Glu382Lys)	ARSA	3	1	Delayed motor development	+	−	+	−	+
Adult-onset Krabbe disease	M	57	Not tested[b]		42	0	Spasticity	−	−	−	−	−
Disorders of lipid metabolism												
Cerebrotendinous xanthomatosis	F	52	Homozygous mutations c.776A>G (p.Lys259Arg)	CYP27A1	12	20	Cataract	+	+	+	−	Not examined
Cerebrotendinous xanthomatosis	F	51	Homozygous mutations c.776A>G (p.Lys259Arg)	CYP27A1	6	24	Cataract, diarrhea	+	+	+	−	Not examined
Cerebrotendinous xanthomatosis	M	57	Compound heterozygous mutations c.844+1G>A and c.850A>T (p.Lys284X)	CYP27A1	4	40	Motor developmental delay, cataract	+	+	+	−	+
Cerebrotendinous xanthomatosis	F	57	Compound heterozygous mutations c.844+1G>A and c.850A>T (p.Lys284X)	CYP27A1	6	39	Mental retardation, behavioral problems, cataract	+	+	+	−	+
Disorder of carbohydrate metabolism												
GLUT-1 deficiency	M	17	c.689_691delAGC, p.(Lys230_Leu231delinsMet)	SLC2A1	0	16	Epilepsy	+	+	+	−	−
GLUT-1 deficiency	F	28	c.1G>A (pMet1?)	SLC2A1	0	8	Hypotonia, frequent falling, frontal lobe seizures	+	+	+	−	Not examined

(Continues)

TABLE 1 (Continued)

Diagnosis	Sex	Age (years)	Mutation	Gene	Age of onset (years)	Diagnostic delay (years)	First symptoms	Movement disorders	Psychiatric history	Cognitive impairment	Eye movement abnormalities	
											Described by patient and/or family	Described at first visit neurologist
Disorders of mineral, metal, or vitamin metabolism												
Wilson's disease	M	30	Homozygous mutations c.3207C>A p.(His1069Gln)	ATP7B	25	4	Cognitive failure, psychosis, dystonia	+	+	+	−	+
Wilson's disease	F	67	Not tested		19	0	Dystonia	+	−	−	−	+
Wilson's disease	M	27	Compound heterozygous mutations c.3207C>A p.(His1069Gln) and c.3282C>G p.(Phe1094Leu)	ATP7B	27	0	Hemolytic anemia, bradyfrenia, dystonia	+	−	+	−	+
Wilson's disease	M	37	Compound heterozygous mutations c.19-20del (p.GLn7fs) and c.3504T>A p.(=)	ATP7B	18	17	Dysarthria, later hemolytic anemia	−	−	−	−	NA[a]
Wilson's disease	M	22	Only one mutation found, c.3741_3742dup, p.(Lys1248*0)	ATP7B	22	0	Anxiety since childhood, nausea	−	+	−	−	NA[a]
Wilson's disease	M	27	Compound heterozygous mutations c.3207C>A p.(His1069Gln) and c.3282C>G p.(Phe1094Leu)	ATP7B	27	0	Depression, tremor	+	+	+	−	+
Ataxia with vitamin E deficiency	M	39	Homozygous mutations c.487delT (p.Trp163Glyfs)	TTPA	4	10	Ataxia	+	−	−	−	Not examined
Ataxia with vitamin E deficiency	M	27	Compound heterozygous mutations c.487del(p.[Trp163fs]) and c.513_514insTT(p.[Thr172fs])	TPPA	10	16	Dystonia	+	+	−	−	−

TABLE 1 (Continued)

Diagnosis	Sex	Age (years)	Mutation	Gene	Age of onset (years)	Diagnostic delay (years)	First symptoms	Movement disorders	Psychiatric history	Cognitive impairment	Eye movement abnormalities	
											Described by patient and/or family	Described at first visit neurologist
Disorders of protein metabolism												
Methylmalonic acidemia	F	25	Not tested		0	0	Coma	+	+	+	−	+
Glutaric aciduria type 1	F	50	Compound heterozygous mutations c.482G>A p.(Arg161Gln) and c.1262C>T p.(Ala421Val)	GCDH	0	45	Chorea, dystonia	+	+	−	−	−
Glutaric aciduria type 1	M	12	Not tested		5	NA*	Macrocephaly, hypotonia	+	−	−	−	−
Congenital disorders of glycosylation												
CDG-1G	F	15	Homozygous mutations c.839C>t(p.P280L)	ALG12	1	4	Psychomotor retardation	−	−	+	+	+
Peroxisomal disorders												
Zellweger spectrum disorder	F	39	Homozygous mutations c2528G>A (p.G843D)	PEX1	0	5	Nystamus, visual impairment, delayed motor development	+	−	+	+	+
Zellweger spectrum disorder	M	34	Homozygous mutations c2528G>A (p.G843D)	PEX1	0	1	Visual impairment, delayed motor development	−	−	+	−	Not examined
Neurotransmitter disorders												
Succinic semialdehyde dehydrogenase deficiency	F	18	Compound heterozygous mutations c.803G>A, p.(Gly268Glu) and c.612G>A, p(Trp204*)	ALDH5A1	0	11	Psychomotor retardation	+	−	+	+	−

(Continues)

TABLE 1 (Continued)

Diagnosis	Sex	Age (years)	Mutation	Gene	Age of onset (years)	Diagnostic delay (years)	First symptoms	Movement disorders	Psychiatric history	Cognitive impairment	Eye movement abnormalities	
											Described by patient and/or family	Described at first visit neurologist
Mitochondrial diseases												
Mitochondrial disease	F	42	Compound heterozygous mutations c.2996G>A (p.Cys999Tyr) and c.977C>T (p.Arg267*)	LIG-3	18	23	Recurrent ileus, migraine	+	−	+	−	Not examined
Kearns-Sayre syndrome	F	45	Not found		35	2	Fatigue and ptosis	−	−	−	+	+
Mitochondrial trifunctional protein deficiency	M	20	Compound heterozygous mutations c.556C>G (p.Gln186Glu) and c.1392+1G>A	HADHA	1	4	Weakness	−	−	−	+	Not examined
Mitochondrial trifunctional protein deficiency	M	18	Compound heterozygous mutations c.556C>G (p.Gln186Glu) and c.1392+G>A	HADHA	1	1	Weakness	−	−	+	+	Not examined

[a]No previous neurological examination.
[b]Genetic confirmation in brother.

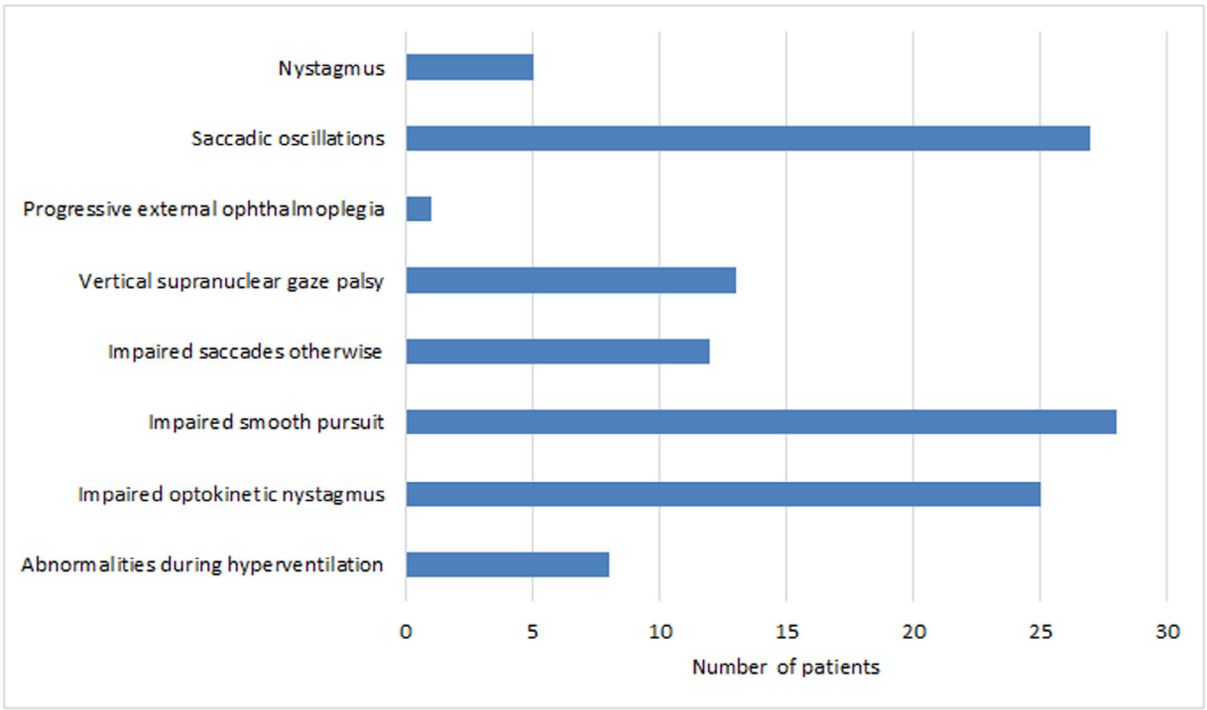

FIGURE 1 Different types of eye movement disorders

gain (alternately too low and too high) in one of them. This latter patient also had an impaired OKN in upward direction.

In three of the six patients with *Wilson's disease*, VOG results indicated saccadic oscillations during rest. An example is shown in Video S5. Saccades were too slow in one patient. Smooth pursuit was impaired in all but one, showing saccadic intrusions (four patients) or square-wave jerks (one patient). In one patient, OKN was severely impaired in horizontal direction and absent in vertical direction. Hyperventilation aggravated square-wave jerks in another patient with also an increase of amplitude.

The two patients with *ataxia with vitamin E deficiency* (AVED) both showed horizontal microsaccadic oscillations at rest. Smooth pursuit, saccades, and OKN were disrupted by these saccadic oscillations, which presented as a pendular nystagmus in one of them. Video S6 shows a hyperventilation-induced ocular flutter and hippus in one of the patients.

We included two patients with *glutaric aciduria type 1* (GA-1), of which one of them was diagnosed during the newborn screening and treated with a lysine-restricted diet since then. This patient showed a latent strabismus, too low gain during smooth pursuit, and very subtle hypermetria during testing saccades. The other patient was diagnosed with GA-1 in her forties and was not treated with a diet. She showed a spontaneous nystagmus to the left which was suppressed by fixation, as can be seen in Video S7. Furthermore, smooth pursuit showed saccadic intrusions (anticipation). In both patients, a vestibular origin of the eye movement abnormalities was suggested, although the vestibular-ocular reflex was not performed.

The patient with a *congenital disorder of glycosylation type Ig* (CDG-1 g) had a history of ptosis and strabismus, for which he underwent surgery. At rest, a drift to the right was still found, with square-wave jerks during fixation. These saccadic intrusions were also found during smooth pursuit and saccades.

Two patients with a *Zellweger spectrum disorder* were included. In one of them, the parents noticed a nystagmus when she was a few months old that eventually disappeared again. Both suffered from reduced vision. Horizontal microsaccadic oscillations were observed at rest, during fixation, and during smooth pursuit. Saccades were not assessable in both patients, in one of them because the initiation of saccades was incorrect, and in the other because the pupil was not detectable by the camera. Vertical OKN was impaired in one patient. This may be due to visual impairment, as the gain of vertical OKN is influenced by binocular disparity.[12]

The included patient with *succinic semialdehyde dehydrogenase deficiency* (SSADH deficiency) had a history of strabismus, and showed saccadic intrusions during neurological examination. These abnormalities were not

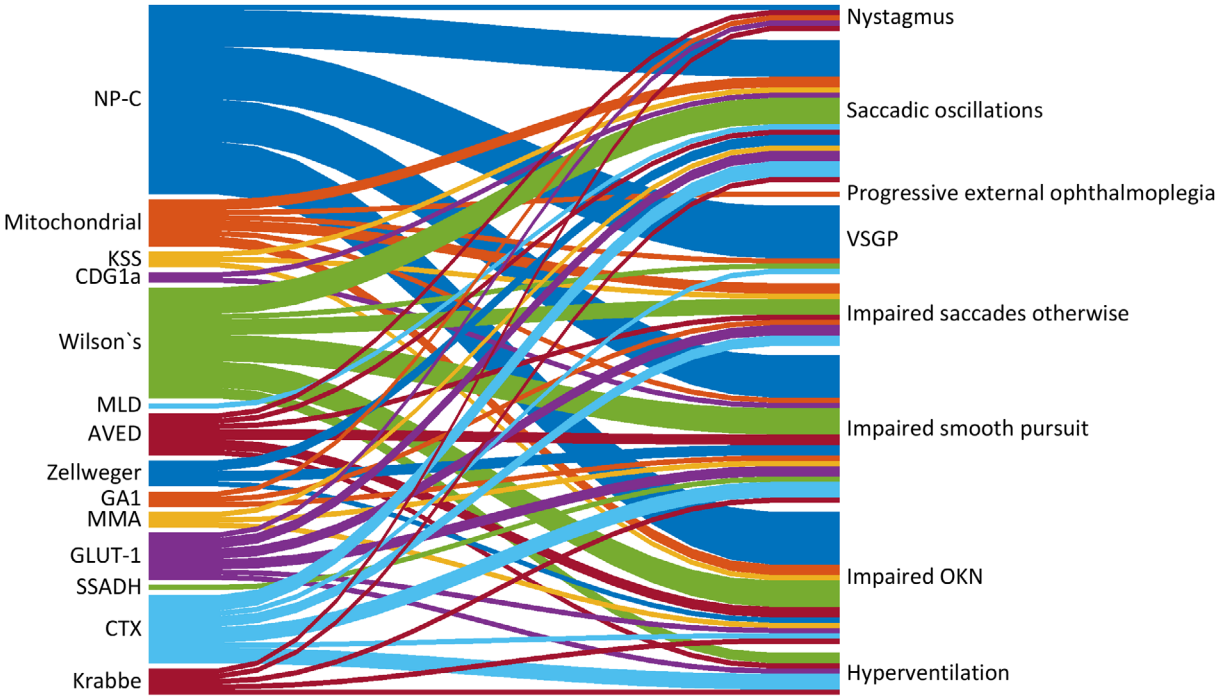

FIGURE 2 Inborn errors of metabolism and associated eye movement disorders. AVED, ataxia with vitamin E deficiency; CTX: cerebrotendinous xanthomatosis; GA1, glutaric aciduria type 1; KSS: Kears–Sayre syndrome, MLD: metachromatic leukodystrophy; MMA: methylmalonic acidemia; NP-C, Niemann-Pick type C; OKN: optokinetic nystagmus; SSADH, succinic semialdehyde dehydrogenase deficiency; VSGP: vertical supranuclear gaze palsy.

present on VOG, in which only catch-up saccades were observed during smooth pursuit, suggesting the influence of fluctuation in attention.

Finally, Figure 2 also shows the results of eye movement investigations in patients with adult-onset *Krabbe disease*, *metachromatic leukodystrophy* (MLD), and *methylmalonic acidemia*. These eye movement abnormalities are not described in detail in the literature earlier. The patients with adult-onset Krabbe disease and MLD showed saccadic oscillations during rest, which is square-wave jerks in the patient with MLD and horizontal microsaccadic oscillations in the patient with adult-onset Krabbe disease. These oscillations interfered with smooth pursuit and saccades in both patients. In the patient with methylmalonic acidemia, micro-opsoclonus was observed during fixation. The gain of smooth pursuit was too low with microsaccadic intrusions, whereas saccades were normal. Gain was also too low during OKN.

3.2 | Movement disorders, psychiatric symptoms, and cognitive impairment

Movement disorders were present in 29 patients (78%). Of these patients, 7 had a single movement disorder, 14 had two movement disorders, and 8 had patients three or more. Dystonia was most frequently present (23 patients), followed by ataxia (18 patients) and myoclonus (12 patients). No relation was found between the presence of a specific type of eye movement disorder and the presence of movement disorders in general nor a specific movement disorder subtype (Supplementary information, Figure S1).

Psychiatric symptoms were present in 14 patients (38%), of which 3 patients had a history of psychosis. In 26 patients (70%) cognitive impairment was present. The presence of cognitive impairment or psychiatric symptoms did not show any significant relation with specific eye movement abnormalities. An overview of the presence of these and other symptoms can be found in Figure S2 of the Supplementary Information.

In the 18 patients with onset during adolescence or adulthood, symptoms that were most frequently present were movement disorders ($n = 14$, 78%), dysarthria ($n = 13$, 72%), cognitive impairment ($n = 12$, 67%), liver and/or spleen abnormalities ($n = 12$, 67%), and psychiatric symptoms ($n = 8$, 44%). Dysarthria was only present in patients with a movement disorder. In the patients with liver and/or spleen abnormalities, 6 were diagnosed with Wilson's disease, 5 with NP-C, and 1 with a mitochondrial disorder. In the patients with NP-C, these abnormalities were mainly characterized by prolonged

TABLE 2 Eye movement abnormalities in 37 patients with an inborn error of metabolism

Diagnosis	Ptosis	Strabismus	Nystagmus	Saccadic oscillations	Paralytic saccades	Dysmetric saccades	Slow saccades	Impaired smooth pursuit	Impaired optokinetic nystagmus	Abnormalities during hyperventilation
Niemann-Pick type C			1/10	7/10	10/10 (v)		7/10 (h)	8/10	10/10	
Metachromatic leukodystrophy				1/1				NA		NA
Cerebrotendinous xanthomatosis				3/4	1/4 (v)	2/4		3/4	1/4	3/4
GLUT-1 deficiency	1/2		1/2	2/2		1/2	1/2	2/2	1/2	1/1
Wilson's disease				5/6	1/6 (v)	1/6	2/6	5/6	5/6	2/6
Ataxia with vitamin E deficiency			1/2	1/2		1/2		2/2	2/2	1/2
Methylmalonic acidemia		1/1		1/1				1/1	1/1	
Glutaric aciduria type 1		1/2	1/2			1/2		1/2		
CDG-1G	1/1	1/1		1/1				1/1		
Zellweger spectrum disorder		2/2		2/2		NA	NA	2/2	1/2	
Adult-onset Krabbe			1/1					1/1	1/1	1/1
Mitochondrial disease	1/4			3/4	2 (1v, 1PEO)	3/4		1/4	3/4	

Notes: Presented as a proportion of each IEM. h, horizontal; NA, not applicable (not performed or not interpretable) PEO, progressive external ophthalmoplegia; V, vertical.

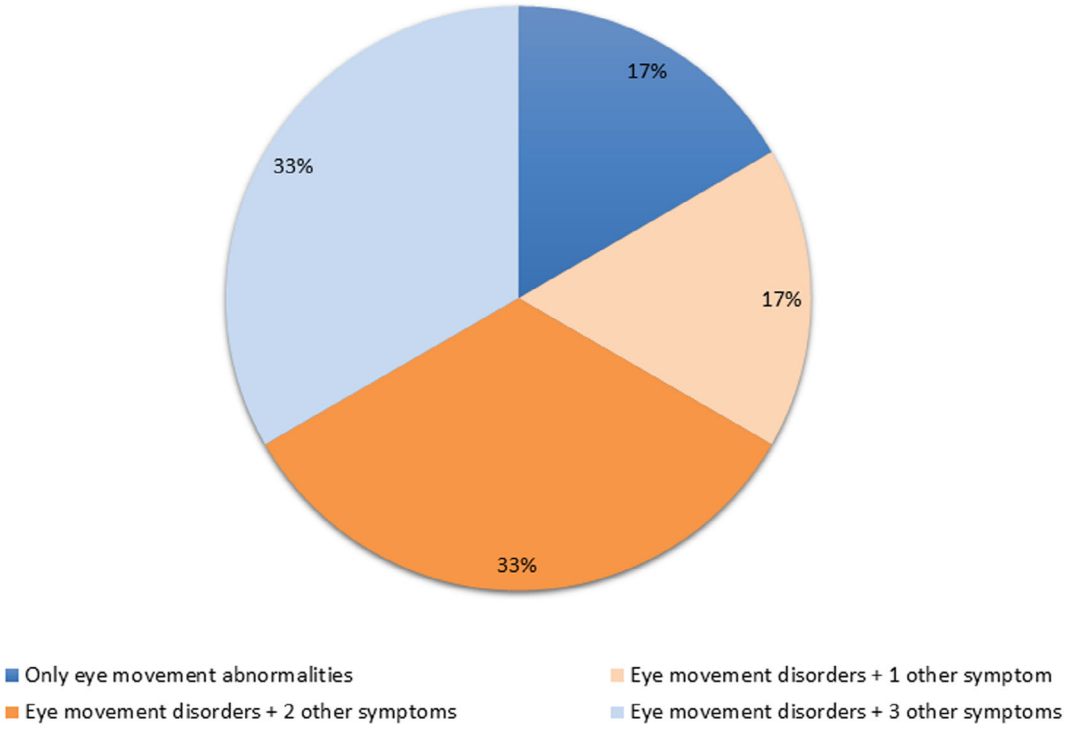

FIGURE 3 Combination of eye movement disorders and other frequent symptoms in late-onset IEMs. Other symptoms include movement disorders, psychiatric symptoms, and cognitive impairment.

jaundice in the neonatal period or by liver/spleen enlargement during the ultrasound (Figure 3).

3.3 | Combination of symptoms in late-onset inborn errors of metabolism

None of the patients presented with an isolated eye movement disorder (Figure 3). Of all the patients with a late-onset IEM, 17% had eye movement abnormalities in combination with movement disorders, psychiatric symptoms, or cognitive impairment. In 33% of the patients, two of these symptoms were present, and another 33% showed all three symptoms. Only 17% presented without one of these features, and among them were patients with adult-onset Krabbe disease, Kearns-Sayre syndrome, and Wilson's disease. All three of them had other neurological or non-neurological symptoms instead.

4 | DISCUSSION

In the current paper, we describe in detail the phenomenology of eye movement abnormalities and other symptoms in 37 patients with an IEM. These eye movement disorders were quantified with VOG and illustrated by videos. Eye movement abnormalities were an early feature in at least 14 patients, as they were reported during the first documented neurological examination. This indicates that examining eye movements can be helpful in the early diagnosis of IEMs, facilitating early treatment when available. Clinical examination of eye movements is not difficult, and can be performed quickly.[8,11,12]

Our results showed that the type of eye movement disorder, with a few exceptions, is often not related to a specific type of IEM. Only in NP-C and Kearns-Sayre syndrome, the observed eye movement disorders are a known characteristic of the IEM.[9,10,13] This heterogeneity may be partially explained by the fact that patients were investigated at different ages and different stages of their disease. However, as earlier described in the literature, many other symptoms are heterogeneous in IEMs as well. This is the case for movement disorders, where the exact type of movement disorder often does not guide into the direction of a specific IEM.[6,14] As movement disorders and eye movement disorders may share an anatomical substrate, for example, cerebellar dysfunction,[15] the variety of eye movement disorders in the same IEM could be expected. However, no clear association was found when eye movement abnormalities were assessed in relation to a specific movement disorder, which may be partially related to the combined movement disorder phenotypes in most of the patients. Our findings

underscore again that symptoms, including eye movement disorders, can be very heterogeneous in IEMs, and this in itself can be considered as an important characteristic of IEMs.

The exact underlying pathophysiological substrate of the eye movement disorders is unknown for many IEMs. An exception to this is NP-C, where histopathological examinations showed damage of the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) in the mid-brain, leading to an isolated vertical saccadic paresis.[9] In our cohort, all the included patients with NP-C showed indeed a VSGP during examination of saccades. This is higher than reported in the literature, where VSGP is described in 66% of the NP-C patients.[10] This difference might be due to the fact that a VSGP may initially only be present during (self-initiated) saccades, as smooth pursuit gets affected in progressive disease.[16] Eye movement disorders are also well described in patients with mitochondrial disease: the extraocular muscles are extremely vulnerable to mitochondrial dysfunction leading to progressive external ophthalmoplegia, which was also found in our patient with Kearns-Sayre syndrome.[17]

Vestibular dysfunction is also related to eye movement disorders, and may be present in some IEMs. In certain mitochondrial diseases, sensorineural hearing loss is associated with a vestibular disorder, although this was not the case in our included patients.[18] Interestingly, in the two patients with GA-1, a vestibular origin of the eye movement disorder was suggested, even though the VOG protocol did not contain examination of the vestibular-ocular reflex. Vestibular involvement causing vertigo is recently described in patients with late-onset GA-1 and vertigo, but the role of the vestibular system still needs to be elucidated for many other IEMs.[19] Therefore, we recommend analysis of the vestibular system in patients with IEMs.

In addition, we showed that hyperventilation could induce very prominent eye movement disorders. Hyperventilation was added to the protocol because it can provoke abnormal eye movements in patients with vestibular disease or cerebellar disorders.[12] This may be mediated through the effect on voltage-gated calcium channels, which are sensitive to pH changes. Hyperventilation-induced alkalosis may cause abnormal activity of these channels, leading to nystagmus.[20–22] Cerebellar involvement is common in IEMs and may lead to ataxia and abnormal eye movements, but abnormalities during hyperventilation are not described earlier in IEMs. We found hyperventilation-induced oscillations in 8 of the 34 tested patients. Some of the included IEMs that showed hyperventilation-induced eye movement disorders are indeed strongly associated with cerebellar impairment, such as CTX and AVED, and these patients also showed ataxia. However, this association is less clear for the other disorders. Interestingly, among them is a patient with Wilson's disease without other neurological involvement.

Other factors that are associated with eye movement abnormalities according to the literature include cognitive impairment and psychiatric symptoms. In our study, no significant relation was found between these symptoms and eye movement disorders. In addition, also visual disturbances may cause eye movement disorders, and in particular nystagmus is frequently described.[12] The three patients with visual impairment (two with a Zellweger spectrum disorder and one with a mitochondrial disorder) did show saccadic oscillations in rest, which may be (partially) caused by the visual disturbances.

It is not only important to recognize eye movement disorders as they may serve as an additional clue in the diagnosis of an IEM, it is also important to recognize them because they sometimes can be treated when they interfere with normal vision. Downbeat and upbeat nystagmus can be found in disorders affecting the brainstem or the cerebellum, and were present in two of the included patients. It can lead to oscillopsia with reduced visual acuity, and therefore increase the risk of falls. This is even more a problem in patients who also have an impaired balance due to movement disorders. Treatment of this specific type of nystagmus is possible with aminopyridines or baclofen.[23,24] In our cohort, VSGP interfered most with daily life, as patients mentioned difficulties during walking outside or performing hobbies, such as playing pianos. Unfortunately, no treatment is available for VSGP yet.

Although we aimed to perform a very comprehensive study on eye movement abnormalities in selected IEMs, our study has some limitations. This is the first big cohort that systematically describes eye movements in IEMs, however, only few patients were included of some IEMs. Therefore, it is not possible to generalize the observed eye movement abnormalities to a larger group. This is partially due to the low prevalence of IEMs, but also to the fact that severely affected patients were not capable to undergo a VOG, which requires sitting still and performing specific tasks. This underscores the need for an easier way of measuring eye movements in these patients, and future research to develop this is needed. Furthermore, the results may be influenced by medication. Anti-epileptic drugs, antidepressants, and mood stabilizers, which were frequently used in this cohort, can cause nystagmus, ocular flutter, and opsoclonus. To end, the differential diagnoses of the described eye movement disorders is of course broader than the described IEMs in

this study, and includes also nonmetabolic disorders. VSGP is a very characteristic sign of progressive supranuclear palsy, and progressive ophthalmoplegia can be found in other energy metabolism disorders as well.[12] However, a systematic approach that involves next-generation sequencing after exclusion of more common acquired or neurodegenerative disorders will lead to the diagnosis of both metabolic and non-metabolic disorders.[4–6]

5 | CONCLUSION

Our results indicate that eye movement disorders may be present early in the course of an IEM, and can be a characteristic symptom. This is in particular the case for patients with NP-C and Kearns-Sayre syndrome. However, apart from these few exceptions, the type of eye movement disorder does not point in the direction of specific IEMs. Symptoms, including eye movement disorders, are very heterogeneous in IEMs, and this variety in symptoms seems to be an important characteristic of IEMs. It is important to note that in adolescents and adults with eye movement disorders, the presence of movement disorders, psychiatric symptoms, or cognitive deficits should raise the suspicion of an underlying IEM, as in our cohort 83% of the late-onset patients presented with one or more of these additional symptoms.

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CONFLICT OF INTEREST

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ETHICS APPROVAL

This study was approved by the medical ethical committee of the University Medical Center Groningen (METc2016/616). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients or parents for being included in the study. Additional informed consent was obtained from all patients for which identifying information is included in this article.

ORCID

Marina A. J. Tijssen https://orcid.org/0000-0001-5783-571X

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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