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Review article

Eye movement disorders in genetic dystonia syndromes: A literature overview

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ABSTRACT

With the growing possibilities in genetic testing, the number of genetic disorders associated with dystonia has constantly increased over the last few years. Accurate phenotyping is crucial to guide and interpret genetic analyses in the search for an etiological diagnosis. Although eye movements examination has proven a valuable tool in the assessment of patients with inherited movement disorders such as ataxia or parkinsonism, less is known about the association between eye movement disorders and genetic dystonia. This study aimed to summarize the most frequent eye movement disorders in monogenetic forms of dystonia as classified by the Movement Disorders Society (MDS). More than sixty genetic disorders causing dystonia were repeatedly associated with eye movement disorders. Among these, 24 are classified as DYT genes, 22 were classified by MDS as having another prominent movement disorder, and 19 are genetic disorders that manifest with dystonia but are not included in the MDS classification. Six different eye movement disorders have consistently been reported (saccadic slowing and supranuclear gaze palsy, saccadic initiation failure and oculomotor apraxia, saccadic dysmetria, oculogyric crisis, nystagmus and ophthalmoplegia). The phenotypic association of each disorder with monogenic dystonic diseases, as well as the possible underlying pathophysiological mechanisms, is described here. Our findings suggest that eye movement disorders, along with the movement phenotype, may help delineate subgroups of dystonia by reflecting disruptions in specific brain networks. Therefore, eye movement examination is a crucial part of the neurological evaluation, providing valuable insights into patients with inherited forms of dystonia.

1. Introduction

Dystonia is defined as a hyperkinetic movement disorder (MD) characterized by sustained or intermittent muscle contractions causing abnormal and often repetitive movements and/or postures. It is etiologically classified as inherited, acquired, or idiopathic [1]. The current view states that dystonia is a network disorder, with dystonic symptoms arising from dysfunction at cortico-thalamic-basal ganglia level with a possible role for brainstem and cerebellar pathways [2,3].

Our understanding of the genetic background of dystonia is rapidly expanding due to the availability of next generation sequencing (NGS) techniques, with a fast-growing number of new genetic etiologies [4]. In the latest Movement Disorders Society (MDS) classification papers, 59 genes (DYT-genes) are presented manifesting with isolated dystonia or dystonia as the predominant MD [5,6]. Further, NGS has also led to an expansion of a dystonic phenotype in genetic disorders primarily associated with other MDs such as parkinsonism or ataxia (non-DYT genes) [5–8]. To deal with this increasing complexity, detailed phenotyping is warranted to guide and interpret data from genetic analysis [9,10].

Several studies focused on the clinical value of eye movement

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disorders (EMDs) in genetic MD [11–14]. EMDs may be of help to distinguish among inherited MDs such as ataxia or parkinsonism [13, 14], and even raise the strong suspicion of specific condition as observed with vertical supranuclear gaze palsy in Niemann Pick type C disease [15]. Moreover, EMDs can be the presenting and/or leading sign in several conditions evoking specific groups of disorders [11]. The co-occurrence of dystonia and EMD may expand the knowledge of the functional impact of gene functions and alterations on anatomical level. However, EMDs in patients with inherited forms of dystonia have been less characterized compared to other MDs.

This review aims to summarize the most frequent eye movement abnormalities in monogenetic forms of dystonia, delineating phenotypical and possible converging pathophysiological pathways.

2. Methods

2.1. Search strategy

A literature search for papers concerning EMDs in patients with dystonia due to an inherited disorder was conducted up to August 2024. English written papers were selected from PubMed and through in-paper relevant citations. Detailed search terms can be found in *Supplementary material.*

The first search (Search 1) aimed to detect reports of EMDs in patients with genetic confirmed dystonia caused by 59 isolated, combined and complex DYT-genes, according to the MDS task force classification [5,6], such as DYT/CHOR, DYT/PARK, DYT/ATX.

A second broader search (Search 2), which was performed by combining the same EMD search terms with terms as “dystonia” and “gene*“, included inherited disorders in which dystonia is present in the patient but not the main motor phenotype according to the MDS classification (non-DYT genes) and other genetic disorders that report dystonia as part of the clinical phenotype.

2.2. Selection criteria

Genetically or biochemically (inherited metabolic diseases) confirmed cases were included when the combination of dystonia and EMD were present in at least two patients. Diseases due to large DNA deletion or duplication were excluded from the analysis.

2.3. Phenotypical and pathophysiological associations

For each type of inherited dystonia, the two most frequently associated EMDs were considered and described in the manuscript, but a complete list of EMDs in DYT-associated and other MD associated (non-DYT) genes was generated as well. Furthermore, the presence of typical associations of dystonic and EMD phenotypes were explored, and the underlying molecular and/or brain network dysfunctions were analyzed when possible.

3. Results

A total of 887 papers were retrieved from the literature, of which 288 met the inclusion criteria. Eight different EMDs were repeatedly reported in the genetic syndromes with dystonia. Some EMDs, such as ocular flutter, opsoclonus, square-wave jerks, and smooth pursuit alteration which were inconsistently reported in a few conditions were not further taken into consideration.

Due to clinical and/or pathophysiological similarities, some EMD were grouped together. Slow saccades and supranuclear gaze palsy share the same pathophysiological mechanisms in the brainstem, as well as overlapping involvement of basal ganglia, cerebellum and cortical areas may be involved. Slow saccades may temporally precede a supranuclear gaze palsy in some cases, as so, these EMDs were regarded as one. Further, saccadic initiation failure and oculomotor apraxia have overlapping features: the impairment consists in failure of volitional saccades and failure of both volitional and reflexed saccades, respectively. Being part of the same spectrum with the same neuroanatomical pattern alteration, these features were combined as well [16].

This resulted in six EMDs to be associated with genetic dystonia: 1) Saccadic slowing and supranuclear gaze palsy; 2) Saccadic initiation failure and oculomotor apraxia; 3) Saccadic dysmetria; 4) Oculogyric crisis; 5) Nystagmus; and 6) Ophthalmoplegia.

Search 1 revealed that EMDs were repeatedly reported in 24 of the 59 DYT genes, including 12 DYT, 9 DYT/PARK, 2 DYT/CHOR, and 1 DYT/ATX genes. Search 2 resulted in EMDs reported in 41 gene related diseases, including 22 other MD associated (non-DYT) genes from the MDS classification [ATX (11), MYC/ATX (1), PARK (3), paroxysmal MDs (PxMD; 2), PxMD/ATX (1), CHOR (1), disorders with mixed MDs (MxMD; 3). In addition, there were 19 genes found not included in the MDS classification (Fig. 1). A complete list of the genes is reported in Table 1, *and Supplementary material.* The recurrent phenotypical and pathophysiological association of genetic dystonia with specific EMDs with their definition and main anatomical areas involved is shown in Table 2. More detailed results will be discussed separately for every EMD.

3.1. Slow saccades and supranuclear gaze palsy

3.1.1. Phenotypical association

Saccadic slowing and supranuclear gaze palsy were associated with fifteen genetic disorders: presenting with isolated DYT (n = 1, *DYT-KMT2B*), combined DYT (n = 3, DYT/PARK (*PLA2G6-(NBIA)*, *SLC6A3*) and *ATX/DYT-SQSTM1*) and complex DYT (n = 2, *DTY-IRF2BPL and DYT-PANK2-(NBIA)*. In addition, they were reported in 9 non-DYT

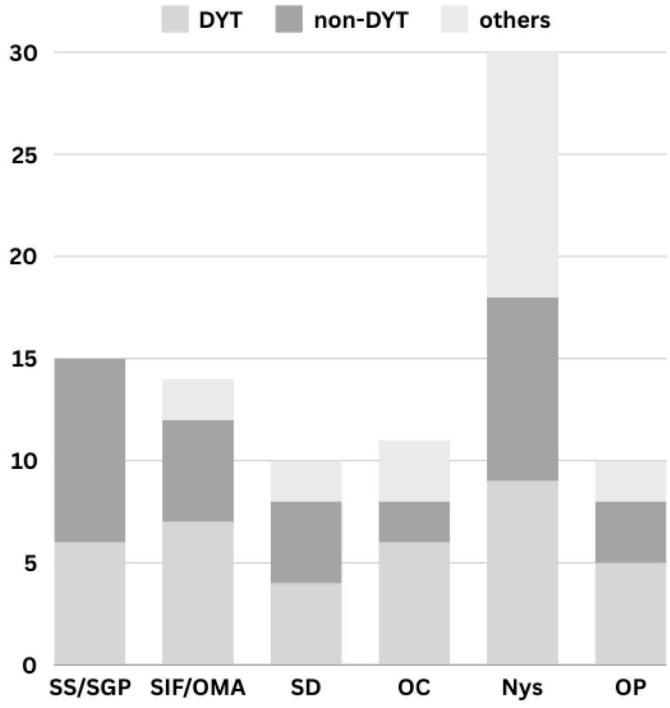

Fig. 1. Fig. 1 shows the number of genes associated with specific eye MD. Genetic disorders have been divided in three groups according to the clinical phenotype. **DYT**: DYT genes according to MDS classification, including genes with 2 label (i.e. DYT/CHOR, DYT/PARK); **non-DYT**: Genes listed in MDS classification with other predominant movement disorders; 3) **others**: Genes not included in MDS classification that manifest with dystonia.
SS/SGP: Slow saccades and supranuclear gaze palsy. SIF/OMA: Saccadic initiation failure/Oculomotor Apraxia. SD: Saccadic Dysmetria. Nys: Nystagmus, OC: Oculogyric crises. OP: Ophthalmoplegia.

Table 1
Complete list of monogenic disorders associated to dystonia and EMDs.

GENE	INHERITANCE	OMIM	SS/SGP	SIF/OMA	SD	OC	NYS	OP
DYT-ATP7B	AR	606882	+	++	++			
DYT-DDC	AR	107930				++		
DYT-EIF2AK2	AD, AR	176871					++	
DYT-IRF2BPL	AD	611720	++				++	
DYT-KMT2B	AD	606834	++	++	+		+	
DYT-MECR	AR	608205					++	
DYT-OPA1	AD	165500					++	++
DYT-PANK2	AR	606157	++		++		+	
DYT-SLC19A3	AR	606152					++	++
DYT-SUCLA2	AR	603921						++
DYT-TOR1A	AD, AR (rare)	605204		++ **(AR)**			+	++
DYT-TUBB4A	AD	602662		+		++	++	
DYT/PARK-ATP1A3	AD	182350				++	++	
DYT/PARK-GCH1	AD, AR	600225				++		
DYT/PARK-GLB1	AR	611458					++	
DYT/PARK-PLA2G6	AR	603604	++			+	++	
DYT/PARK-SLC30A10	AR	611146		++				
DYT/PARK-SLC6A3	AR	126455	++	++		+		
DYT/PARK-SPR	AR	182125				++		
DYT/PARK-TAF1	X-L	313650		++	++			
DYT/PARK-TH	AR	191290				++		
DYT/CHOR-GCDH	AR	608801					++	
DYT/CHOR-HPRT1	X-L	308000		++	++			
DYT/ATX-SQSTM1	AR	601530	++	+			+	++
ATX -APTX (AOA1)	AR	606350		++				++
ATX-AFG3L	AR	604581		++				
ATX-ATM	AR	607585		++	+		++	
ATX-ATXN1	AD	601556	+		++		++	
ATX -ATXN2	AD	601517	++					++
ATX -ATXN3	AD	607047	++		+		++	
ATX-DAB1	AD	603448			++		++	
ATX-MRE11	AR	600814		++				
ATX -NPC	AR	607623	++					
ATX-SETX (AOA2)	AR	608465		++			++	
ATX -TBP	AD	600075			++			
MYC/ATX -CSTB	AR	601145		++				
PXMD/ATX-CACNA1A	AD	601011					++	
PXMD-SLC2A1	AD, AR (rare)	138140				++	++	
PXMD-ECHS1	AR	602292					++	
PARK-DCTN1	AD	601143	++					
PARK-GBA1	AR	606463	++					++
PARK-SYNJ1	AR	604297	++					
CHOR-VPS13A	AR	605978	++		++			
MXMD-ATP13A2	AR	610513	++			++		
MXMD-POLG	AR, AD (Rare)	174763						++
MXMD-ADCY5	AD, AR (rare)	600293	++	++				
PNKP (AOA4)	AR	605610		++	++			
HSP-AP5Z1	AR	613653			++			
AARS2	AR	612035					++	
HIBCH	AR	610690					++	
MAG	AR	159460					++	
DEGS1	AR	615843					++	
DLG4	AD	602887					++	
DRD2	AD	126450		++				
GNB1	AD	139380	+				++	++
GRIN1	AD, AR	138249				++		
HIKESHI	AR	614908					++	
MOCS1	AR	603707					++	
MOCS2	AR	603708					++	
PURA	AD	600473					++	
PTCD3	AR	614918					++	
SHQ1	AR	613663				++		
SLC18A2	AR	193001				++		
VPS41	AR	605485					++	
mt*DNA*	Maternally	–						++

X-L: X-linked; SS: slow saccades; SGP: supranuclear gaze palsy; SIF: saccadic initiation failure; OMA: oculomotor apraxia; SD: saccadic dysmetria; OC: oculogyric crisis; Nys: nystagmus; OP: ophthalmoplegia: ++: the two most common EMDs, reported in the main text: +: other EMDs reported in literature. References for each gene in the table can be found in Supplementary material.

genes, including ATX-genes (n = 3, *ATXN2, ATXN3, NPC1*), PARK-genes (n = 3, *DCTN1, GBA1, SYNJ1*), CHOR-gene (n = 1, *VPS13A*), and MxMD (n = 2, *ADCY5, ATP13A2*). Hence, the combination of slow saccades or supranuclear gaze palsy and dystonia is reported in isolated and combined dystonia genes as well as non-DYT genes (mainly ATX- and PARK-genes).

Table 2
Definition and principal anatomical involvement of each eye movement disorders, followed by their phenotypical and pathophysiological associations.

EMDs	Description	Main anatomical involved structures	Recurrent DYT-Genes	Recurrent Non DYT-Genes	Recurrent pathophysiological mechanisms or group of disorders
Slow Saccades[a]	Disorders of saccadic velocity. Saccades are slow, but range of motion is normal.	Brainstem (Superior Colliculus)	DYT	ATX, PARK	Lysosomal and endosomal disorders /NBIA
Supranuclear gaze palsy[a]	Eye movements are slow, and range of motion is limited. May affect selectively saccades or both saccades and smooth pursuit Range of motion is overcome with the doll's eye maneuver.	Brainstem			
Saccadic Initiation Failure[b]	Disorders in saccades initiation. Voluntary and involuntary saccades are delayed in initiation.	Cerebellum Superior Colliculus Basal Ganglia	DYT, DYT/PARK	ATX	Post-synaptic dopaminergic disorders /DNA repairing system
Oculomotor Apraxia[b]	Disorders in saccade initiation. Voluntary saccades are selectively delayed in initiation.	Frontal eye fields Parietal eye fields Cerebellum			
Saccadic Dysmetria	Disorders of saccadic accuracy. Saccades do not reach target as an early stop (hypometric saccades) or an overshoot (hypermetric saccades) occur. Subsequent small saccadic movements may be seen to reach the target.	Cerebellum	–	ATX	–
Oculogyric Crises	Paroxysmal and tonic upwards deviation of the eyes. Discomfort or pain may occur.	Basal Ganglia	DYT/PARK	–	Neurotransmitters disorders
Nystagmus	Involuntary and rhythmic back and forth movement of the eyes.	Cerebellum	DYT, DYT/PARK	ATX	–
Ophthalmoplegia	Limitation of eye movement range, that is not overcome by the doll's eye maneuver	External ocular muscles	DYT	–	Mitochondrial disorders

a and b have been considered respectively together.
Recurrent DYT-genes and non DYT-genes were considered if at least 3 genetic disorders with the same label (i.e. DYT, DYT/PARK, ATX) were found. EMDs: eye movement disorders.

3.1.2. Pathophysiological association

Anatomically, slow saccades or supranuclear gaze palsy usually point to a brainstem dysfunction, such as the paramedian pontine reticular formation, and rostral interstitial nucleus of medial longitudinal fasciculus (riMLF), respectively generating horizontal and vertical saccades [15,17]. In addition, involvement of cerebellar areas is also possible [17,18].

With regards to the pathophysiological background, slow saccades and supranuclear gaze palsy seem to be frequently associated with disorders affecting (or thought to affect) the endo-lysosomal and autophagy systems *(ATX-NPC, DYT-IRF2BPL, ATX/DYT-SQSTM1, MxMD-ATP13A2 PARK-GBA1 and PARK-SYNJ1)* and neurodegeneration with brain iron accumulation (NBIA) (*DYT-PANK2-(NBIA), DYT/PARK-PLA2G6-(NBIA), ATP13A2*) [4,19,20]. In *ATX-NPC* patients, post-mortem examination showed selective degeneration of riMLF neurons [21]. Moreover, MR-imaging detected bilateral brainstem lesions affecting the mesencephalon and caudal pons in *ATX/DYT-SQSTM1* [22–24], and brainstem atrophy in patients with *DYT-IRF2BPL* [25].

In addition to iron accumulation in NBIA, brainstem atrophy is also seen in *ATP13A2, DYT-PANK2-(NBIA)*, and *DYT/PARK-PLA2G6-(NBIA)* [26,27] disorders. Notably, brain iron accumulation was detected in both *ATX/DYT-SQSTM1* and *DYT-IRF2BPL* [28,29].

Finally, slow saccades with an associated progressive gaze restriction and dystonia can be seen in spinocerebellar ataxia type 2 (*ATX-ATXN2*), and 3 (*ATX-ATXN3*). Brainstem lesions, particularly affecting mesencephalic excitatory burst neurons, were reported to be responsible for this ocular manifestation in both these genetic disorders [19,20].

3.1.3. Conclusion

Slow saccades and supranuclear gaze palsy can be seen in a broad range of dystonic phenotypes including DYT and non-DYT genes, without any specific phenotypic associations. These EMDs may suggest the presence of disorders involved in the endo-lysosomal and autophagy pathway or NBIA, with anatomical lesions of the mesencephalon.

3.2. Saccadic initiation failure and oculomotor apraxia

3.2.1. Phenotypical association

Saccadic initiation failure and oculomotor apraxia were associated with 14 disorders, including 7 DYT-gene defects as isolated DYT (*KMT2B, and TOR1A*), combined DYT (*DYT/CHOR-HPRT1*, and DYT/PARK-genes (*SLC6A3, SLC30A10, TAF1*)) and complex *DYT-ATP7B*. They were also reported consistently in non-DYT genes, such as ATX-genes (*AFG3L2*, *ATM, ATPX1, MRE11A, PNKP, SETX*), *MYC/ATX-CSTB*, *MxMD-ADCY5*and in one non-MDS classified gene, (*DRD2)*. In conclusion, saccadic initiation failure and oculomotor apraxia are mainly associated with DYT/PARK genes, pure DYT-genes, but also several ataxic genes.

3.2.2. Pathophysiological association

Oculomotor apraxia results from hemispheric lesions affecting the cortical eye-fields and basal ganglia [17). Saccadic initiation failure may result from lesions affecting several brain areas such as the superior colliculus or deep cerebellar nuclei [17].

The superior colliculus is involved in the generation and initiation of saccades, through activation of brainstem excitatory burst neurons [29]. The superior colliculus is thought to be inhibited by substantia nigra pars compacta [17,29]. In this light, it can be speculated that dysfunction in dopaminergic pathway may cause an imbalance of superior colliculus input, resulting in a delay in the generation of saccades. This may account for saccadic initiation failure observed in individuals with genetic disorders involving the striatal post-synaptic dopaminergic signaling such as *DRD2*, *MxMD-ADCY5*, and possibly *DYT/CH-OR-HPRT1* [30].

Other disorders sharing a common pathophysiological mechanism are represented by genetic disorders involved in DNA break repair systems (*ATX-APTX1, ATX-ATM, ATX-SETX, ATX-PNKP*) [31]. In this group of disorders, a significant loss of cerebellar Purkinje cells is consistently observed, which may contribute to the development of oculomotor apraxia [32]. Furthermore, dysfunction of these cerebellar cells has been implicated in the pathophysiological network underlying dystonia. [33,

34].

3.2.3. Conclusion

There is no clear phenotypical association of saccadic initiation failure and oculomotor apraxia and dystonia. For the latter, while the precise mechanisms remain unclear, the involvement of Purkinje cell impairment appears to be a key feature shared across conditions.

Disorders affecting post-synaptic dopamine signaling or DNA repair system may lead to developing saccadic initiation failure and oculomotor apraxia in combination with dystonia through different mechanisms.

3.3. Saccadic dysmetria

3.3.1. Phenotypical association

Saccadic dysmetria is associated with 10 dystonic disorders, including 4 DYT-genes. Hypometric saccades have been reported in complex dystonia (*DYT-ATP7B, DYT-PANK2-(NBIA)*), 1 combined dystonia *DYT/PARK-TAF1*, and 1 complex dystonia *DYT/CHOR-HPRT1*. Non-DYT genes associated with saccadic dysmetria are *CHOR-VPS13A*, *ATX-TBP, ATX-DAB1, PNKP* and *HSP-AP5Z1*. Hypermetric saccades have been described in *ATX-TBP and ATX-ATXN1* [35–37].

3.3.2. Pathophysiological association

Saccadic dysmetria is a hallmark of cerebellar dysfunction [18], potentially linked to lesions in the fastigial nucleus [17]. The largest group of genes (*ATX-ATXN1, ATX-TBP, ATX-DAB1, ATX-PNKP*) is associated with an ataxic phenotype, suggesting that the cerebellar-basal ganglia network may be a common pathophysiological link. However, other mechanisms have also been proposed, including lesions in the mesencephalon (e.g., central mesencephalic reticular formation and superior colliculus) [13,17] and peripheral causes, such as visual defects [17]. Similarly, saccadic hypometria observed in *DYT/PARK-TAF1*and *DYT/CHOR-HPRT1*mutations is thought to result from aberrant basal ganglia activity, possibly interfering with superior colliculus function [38,39].

3.3.3. Conclusion

Both hypometric and hypermetric saccades are reported in dystonic syndromes. Hypometric saccades may be found in DYT-genes, whereas hypermetric saccades should raise the suspicion of a possible cerebellar disorder presenting with dystonia. Hypometric saccades are less specific in terms of anatomical localization, as they can origin along the whole saccadic pathways (cerebellum, brainstem, cerebellar cortex, white matter and basal ganglia). Accordingly, hypometria in some DYT-genes may originate from altered superior colliculus activity [38,39].

3.4. Oculogyric crises

3.4.1. Phenotypical association

Oculogyric crisis is associated with 11 different genetic disorders, of which 6 DYT-genes [4 *DYT/PARK*-genes (*ATP1A3, GCH1, SPR, TH*) and 2 DYT-genes (*DDC, TUBB4A*)], 2 non-DYT genes (*MxMD-ATP13A2, PxMD-SLC2A1*), and 3 conditions not listed in the current MDS classification (*SLC18A2*, *SHQ1* and *GRIN1*).

3.4.2. Pathophysiological association

The pathophysiological mechanisms underlying oculogyric crises remain elusive, although a hypodopaminergic state (i.e., blockage of the dopamine receptor or a defective dopamine metabolism) is consistently associated with this sign [40]. Accordingly, 6 of the reported dystonic diseases with oculogyric crises are inherited disorders of monoamine neurotransmitters synthesis (iMND) (AR and AD *DYT/PARK-GCH1, DYT/PARK-TH, DYT/PARK-SPR, DYT-DDC, and SLC18A2*). This large group of conditions is among the most frequent genetic cause of early onset dystonia-parkinsonism during infancy and childhood, and results from disorders of synthesis and trafficking of catecholamine and serotonin [41]. Some of the disorders of neurotransmitter synthesis show significant improvement on disease-specific treatment/dopamine suppletion. Due to the non-progressive course for many of these conditions, they may be misdiagnosed as cerebral palsy so delaying diagnosis and treatment [41,42]. The occurrence of oculogyric crisis may be an important clinical clue to differentiate iMND from cerebral palsy [43].

Oculogyric crisis has been reported in other genetic MD such as *DYT/PARK-ATP1A3, MxMD-ATP13A2, DYT-DDC, GRIN1, SHQ1* and *DYT-TUBB4A* [40,44–47]. Interestingly, a dopaminergic dysfunction has been hypothesized in *MxMD-ATP13A2*, *GRIN1* and *SHQ1* defects [44,45,48], and low levels of dopamine metabolite in CSF were detected in patients with *DYT/PARK-ATP1A3, SHQ1 and DYT-TUBB4A* deficiency [40,46,48,49]. Albeit not consistently, some of these patients with one of the six disorders may benefit from dopamine administration [40,46,50].

3.4.3. Conclusion

The presence of oculogyric crisis is mainly associated with a combined dystonia-parkinsonism phenotype and points towards a neurochemical or anatomical dopaminergic dysfunction. Recognition of oculogyric crisis is crucial as it can be considered as a key sign to recognition of potentially treatable iMND.

3.5. Nystagmus

3.5.1. Phenotypical association

Nystagmus was associated with 30 disorders, of which 10 DYT-genes: isolated DYT (*EIF2AK2*), complex DYT (*IRF2BPL, MECR, OPA1, SLC19A3, TUBB4A*), and combined dystonia syndromes as DYT/PARK (*ATP1A3, GLB1, PLA2G6-(NBIA)*), DYT/CHOR (*GCDH*). In addition, nystagmus has been reported in 11 non-DYT genes: ATX-genes (*ATM, ATXN1, ATXN3, DAB1, SETX*), 2 genes associated with PxMD (*ECHS1, SLC2A1*), 1 ATX/PxMD-gene (*CACNA1A*), and *AARS2, HIBCH, MAG* (listed in hereditary ataxia group [6], and in 9 non-MDS genes (*DEGS1, DLG4, GNB1, HIKESHI, MOCS1, MOCS2, PTCD3, PURA, VPS41*).

3.5.2. Pathophysiological association

The underlying pathophysiological mechanisms of nystagmus are broad. Nystagmus can result from central (i.e., cerebellar or white matter lesions) or peripheral causes (visual failure due to optic atrophy or retinal changes, or vestibular lesions) [11,51]. Analogously, some of the associated disorders are predicted to primarily affect the cerebellum (*ATX-SETX, ATX-ATM, ATX/PxMD-CACNA1A, ATX-ATXN1, ATX-ATXN3, ATX-DAB1*) but also white matter (*DYT-TUBB4A, DYT-EIF2AK2, MAG, AARS2, HIKESHI, PURA*). In addition, nystagmus may result from visual problems in some disorders (i.e., *DYT-OPA1, DYT-EIF2AK2, DLG4, MECR, MOCS*).

3.5.3. Conclusion

Although nystagmus is frequent in patients with genetic dystonia, this is associated with many other non-DYT-genes. The presence of nystagmus in dystonia should therefore raise suspicion of disorders usually presenting with different MD (especially ataxia or paroxysmal dyskinesias). The pathological background is broad, possibly involving cerebellum, white matter lesions, visual cortex, ocular and vestibular impairment.

3.6. Ophthalmoplegia

3.6.1. Phenotypical association

Ophthalmoplegia was associated with 11 disorders, of which 4 DYT-genes (*DYT-TOR1A, DYT-SLC19A3, DYT-SUCLA2, DYT-OPA1*), 1 combined dystonia and ataxia (*ATX/DYT-SQSTM1*), 4 non-DYT genes phenotype (*ATX-ATXN2, ATX-APTX1, PARK-GBA1, MxMD-POLG*) and a few non-classified genes (*GNB1,* and mt-DNA disorders).

3.6.2. Pathophysiological association

Ophthalmoplegia is associated with cellular energy failure and mitochondrial disorders [11]. This may be due to the high metabolic requirement of the external eye muscles which are implied in a fast and precise control of eye motility control [52] and, therefore, particularly rich in mitochondria and susceptible to energy failure [52].

Accordingly, this group includes disorders affecting primarily mitochondrial function (*DYT-OPA1, DYT-SUCLA2, POLG and mt-DNA disorders*) or an inborn error of vitamin metabolism or transport as well as other neurometabolic disorders (*DYT-SLC19A3, PARK-GBA1*) [53].

3.6.3. Conclusion

There is no clear phenotypical association between ophthalmoplegia and dystonic syndromes, but the presence of ophthalmoplegia in a dystonic patient should raise the suspicion of a neurometabolic disorder.

4. Discussion

This review aimed to summarize the most frequent EMDs reported in monogenetic causes of dystonia, as well in disorders where dystonia is the main phenotype as in those where dystonia is less prominent. In addition, phenotypical and etiological associations were described. By doing so, we suggest that converging pathophysiological pathways related to dystonia and EMD could suggest specific brain networks involved in the disease process.

4.1. Phenotypical association of eye movement disorders in genetic dystonia

Our review shows that EMDs disorders are a frequent part of the clinical phenotype in genetic dystonia, with EMDs reported in almost half of the 59 DYT genes. For these DYT-genes, no clear association was found between the type of EMD and dystonic phenotype as classified in the MDS classification, with exception of oculogyric crisis and the dystonia-parkinsonism phenotype.

Nevertheless, careful detection of EMDs may help to distinguish dystonic syndromes. For example, the observation of slow saccades in patients with isolated dystonia may point to *DYT-KMT2B* rather than *DYT-HPCA* or *DYT-THAP1* where eye movements are not affected [54]. Saccadic initiation failure and saccadic dysmetria may suggest an underlying DYT/CHOR-gene, such as *DYT/CHOR-HPRT1*, in a patient with combined chorea-dystonia. The occurrence of oculogyric crisis should point a specific group of dopamine deficiencies [11,41]. Therefore, a careful and systematical eye movements examination across genetic dystonia patients could provide additional meaningful insights.

The coexistence of EMDs and dystonia was also reported in 22 non-DYT genes, most frequently ATX genes that were associated with nystagmus, saccadic initiation failure and oculomotor apraxia, slow saccades and supranuclear gaze palsy, and dysmetric saccades. Over the years, the involvement of the cerebellum in dystonia has gained attention [55,56]. Atypical phenotypes of ATX-genes have been reported presenting with prominent dystonia, which may make a correct diagnosis challenging [57–59]. Again, the examination of eye movements is of added value and may help to pinpoint a specific group of disorders. The observation of oculomotor apraxia may point for autosomal recessive conditions (*ATX-ATM, ATX-SETX, ATX-ATPX*) rather than autosomal dominant (*ATX-TBP, ATX-ATXN1, ATX-DAB1*) that instead show saccadic dysmetria.

4.2. Pathophysiological associations

The occurrence of EMDs is known to be associated with specific pathological mechanisms as shown for oculogyric crisis in monoamine neurotransmitter disorders [43], and ophthalmoplegia in mitochondrial disorders [11,40,52].

Interestingly, this review suggests a possible association of slow saccades and supranuclear gaze palsy with NBIA, which might be due to described changes of brainstem structures [20–26]. In addition, saccadic initiation failure and oculomotor apraxia may point to striatal post-synaptic dopaminergic signaling and DNA-break repairing systems. These two mechanisms may lead to a similar EMD through different mechanisms, possibly involving the basal ganglia in the first case, and cerebellum in the latter [32]. For nystagmus, a clear converging pathophysiological pathway could not be determined due to the heterogenous pathophysiological mechanisms of nystagmus.

Classifying the genetic disorders according to a single main pathophysiological mechanism may be an oversimplification of disorders with a complex and/or still largely unknown pathophysiology. However, this manuscript aims to serve as a research framework for understanding the pathophysiological associations between eye movement disorders and genetic dystonia among other phenotypical characteristics, rather than as a diagnostic guide for clinical practice.

4.3. Limitations of eye movement examination

The EMD phenotype across such a broad genetic spectrum of diseases is challenging to link to specific etiological presentations. This review aimed to find potential common pathophysiological pathways. For this reason, we acknowledge the presence of certain limitations in our approach. The recognition of EMDs in patients with complex MDs can be challenging and may show inter-observer variability. To discriminate between EMDs and to come to a proper classification, a structured eye movement examination can be very helpful and be done in a short amount of time [11]. In addition, video recordings may be helpful in paroxysmal EMDs such as oculogyric crises. A quantitative measure of these EMDs is the gold standard but was not available in most cases published in the literature. In addition, it can be quite challenging and even infeasible in patients with dystonia as this gold standard (video-oculography) requires the patients to sit still for 30–45 min. Development of new, easy-applicable methods to quantify eye movements through eye-tracking or video-oculography may provide useful information for the assessment of EMDs, aiding in early detection, further characterization if eye movements and monitoring of therapeutic interventions [60–62], especially in children. In the future, the integration of machine learning to combine eye movement detection with movement phenotypes may improve clinical phenotyping. As our understanding of the association between these factors grows, these tools can be refined to support more accurate diagnosis and monitoring. Lastly, the recognition of new phenotypes associated with genes is rapidly expanding, meaning that our work represents the current state of the art but warrants further exploration and should be revised in light of future discoveries.

5. Conclusion

We have shown that EMDs are frequent in both DYT-disorders and in disorders where dystonia is not the prominent MD. Detailed clinical phenotyping, including a systematic characterization of eye movements in patients with dystonia is important and may lead to gain better insight into the pathophysiology of the disease by identifying the specific brain networks involved in the underlying pathological process.

CRediT authorship contribution statement

Luca Pollini: Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Ilaria Pettenuzzo:** Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Data curation. **Marina A.J. Tijssen:** Writing – review & editing, Visualization, Methodology, Investigation, Conceptualization. **Lisette H. Koens:** Writing – review & editing, Writing – original draft. **Tom J. De Koning:** Writing – review & editing, Writing – original draft. **Vincenzo Leuzzi:** Writing – review & editing, Writing – original draft. **Hendriekje**

Eggink: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2025.107325.

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