Aberrant Interactions Between Basal Ganglia-Cerebellar and Brainstem-Cerebellar Circuits in Dystonia: Insights into Network Disruptions and Gene Therapy Prospects

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Abstract

From the preceding, it may be deduced that coupled dystonia syndromes are different, as are the disease phenotypes caused by the same gene. There are different starting ages, different symptom presentations, different disease manifestations, and atypical presentations. Accepting clinical exome sequencing and gene panels in the diagnosis of genetic diseases has also widened genotypes and phenotypes. It's critical to stay on top of the latest advances in genetic technology and to comprehend the full scope of these fascinating diseases. Online resources are updated on a regular basis and incorporate genetic and phenotypic data. Neurophysiology and imaging methods are important for better phenotyping and complementing clinical outcomes. Recent research suggests that the MYC/DYT-SGCE, XDP, and RDP basal ganglia-cerebellar and brainstem-cerebellar circuits may interact abnormally. Linking network interruptions to cellular failure will help us better grasp the underlying pathophysiology and teach us new treatment strategies.

Introduction

Monogenic mixed dystonias are a varied category of illnesses, when dystonia accompanies another movement disease. In dopa-responsive dystonia (DYT/PARK-GCH1), rapid-onset dystonia-parkinsonism (DYT/PARK-ATP1A3), X-linked dystonia-parkinsonism (XDP, DYT/PARK-TAF1) and young-onset dystonia-parkinsonism (DYT/PARK-PRKRA), parkinsonic characteristics accompany dystonia. Apart from sharing a phenotypic feature, dystonia and parkinsonism have nothing in common in terms of genetics or molecular processes.Dystonia occurs in association with myoclonus in MYC/DYT-SGCE and MYC/DYT-KCTD17 and psychiatric comorbidity in the former. Besides the variability across distinct monogenic combined dystonia groupings, these genetic illnesses are characterized by considerable inter-and intra-family and inter-individual phenotypic variances. Early age, familial penetration, and illness manifestation differ, yet certain general traits might be identified by comprehensive phenotyping. Interestingly, recent neurophysiological and imaging studies suggest that common mechanisms exist for some of the combined dystonias, making them valuable model diseases for genotype–phenotype–neurophysiological correlations that may be useful for other genetically undefined syndromes of dystonia or general movement disorders. In the combined dystonia syndromes, we present updates on clinical characteristics, neurophysiological data, and genotype-phenotype relationships.

Parkinsonism Dystonia

Dystonia Dopa-responsive

DYT/PARK-GCH1 (Dopa-responsive dystonia, DYT5, OMIM # 128230) commonly begins in infancy (median age 8 years), commonly as a foot dystonia, which subsequently expands slowly and reaches a plateau as a widespread adolescent dystonia. While this is the conventional depiction, the literature shows a broad range of ages at the beginning (0–68 years) (mdsgene.org). Besides dystonia, most patients have minor parkinsonian symptoms such as bradykinesia, tremor, and stiffness. Many individuals demonstrate diurnal changes in their symptoms, likely due to fluctuating dopamine amounts (Segawa 2011). Monoalellic genetic variations in guanosine triphosphate cyclohydrolase 1 (GCH1) are the most prevalent cause of autosomal dopa-responsive dystonia (DRD). Penetration is lowered by roughly 50% (Ichinose et al. 1994). Women have higher penetration than males, and are up to four times as likely to have illness symptoms (Furukawa et al. 1998; Steinberger et al. 1998). All ethnicities reported DYT/PARK-GCH1.

GCH1 gene genes for guanosine triphosphate cyclohydrolase 1, an enzyme catalyzing the rate-limiting step in tetrahydrobiopterine biosynthesis (BH4) (Ichinose et al. 1995). BH4 is an important cofactor of tyrosine and tryptophan hydroxylase, catalyzing dopamine and serotonin production accordingly. The ensuing neurotransmitter abnormalities create motor and non-motor characteristics that are often part of the DRD phenotype and include anxiety disorders, depression and sleep difficulties (Tadic et al. 2012; Bruggemann et al. 2014).

If left untreated, motor symptoms lead to severe symptom progression and major impairment. This is particularly sad when individuals demonstrate remarkable responsiveness to L-dopa due to the metabolism of the illness. It is thus highly advised that each dystonia beginning in infancy be evaluated with an L-dopa test (if required up to a maximum daily dose of 3/200 mg daily for up to 8 weeks, recommendation of the German Neurology Guidelines for Dystonia, Volkmann Jens) (Malek et al. 2015). Even low dosages of L-dopa (< 300 mg daily) are adequate to keep patients in a markedly better condition (Jankovic 2006). Importantly, treatment response should be routinely checked since many individuals have persistent indications with insufficient L-dopa dosages (Tadic et al. 2012). Dyskinesias are primarily observed after therapy commencement and can be decreased by dose decrease. However, some individuals may report modest dyskinetic movements upon careful evaluation (Lopez-Laso et al. 2012; Bendi et al. 2018).

DYT/PARK-GCH1 genetic variation covers the length of the GCH1 gene, with no obvious location-based genotype-phenotype link or damaged protein domain. There are 134 distinct genetic coding variations documented in DRD patients according to MDSGene compilation, an online reference compiling research on genetic variations of dystonia and parkinsonism (mdsgene.org). Up to three-fourths of variation is reported once while others are recurring; one nonsense protein truncating variant (PTV) has been observed in exon 1, c.181G > T (RefSeq NM 000161.3) (p.Glu61 *) in at least eight families/individuals. Variant categories include single-nucleotide variation (SNVs) leading to abuse and absurd protein modifications, as well as significant structural variations involving exon deletion or the whole gene (Furukawa et al. 1996, 2000; Steinberger et al. 2007).

GCH1 variation in dopa-responsive dystonia. Genetic variants were collected from records in MDSGene (mdsgene.org) and are depicted by gene location (exon), variant type (e.g., missense, indel, frameshift, nonsense, splicing) and literature case report frequency, with more commonly occurring variations indicated by bigger symbols. Variants are also compared using their CADD-Phred scores (cadd.gs.washington.edu), a pathogenicity metric based on numerous bioinformatic annotations. With a CADD Phred score of 22.5, the most common variation of DYT/PARK-GCH1 is a single-nucleotide mutation resulting in a premature stop codon in exon 1, c.181G > T (p.Glu61 *).A CADD-Phred score of > 20 shows that SNV is among the most harmful variations in the human genome.

There is clear phenotypic diversity in several DRD families (Grimes et al. 2002). Additionally, GCH1 variant carriers may have parkinsonism comparable to idiopathic Parkinson's disease (PD), which develops later in life (Mencacci et al. 2014; Yoshino et al. 2018). These people frequently display a benign type of PD with low Hoehn and Yahr and UPDRS III scores across extended periods of illness, and require lower doses of L-dopa to regulate symptoms (Yoshino et al. 2018; Shin et al. 2020).

There are also people with neurodegenerative PD-like symptoms, such as severe treatment fluctuations, L-dopa-induced dyskinesias, clinical evidence of neurodegeneration, and pathological dopamine transporter scans (Mencacci et al. 2014; Weissbach and Klein 2014). It is uncertain if they belong to the DYT/PARK-GCH1 phenotypic spectrum or whether genetic diversity in GCH1 acts as a risk factor for neurodegenerative parkinsonism (Rudakou et al. 2019; Blauwendraat et al. 2019).

However, in most people with classical DYT/PARK-GCH1, the capacity to store and release dopamine seems unimpaired, with typical structural and metabolic imaging results (Nygaard et al. 1992; O'Sullivan et al. 2001; Shin et al. 2020). Clinical neurophysiological research has demonstrated that an acute 24-hour dopamine deficit does not significantly affect clinical symptoms or diminish the connection between premotor and motor brain areas when evaluated using transcranial magnetic stimulation (TMS) (Weissbach et al. 2015a). Previous TMS investigations showed normal and diminished intracortical inhibition of the primary motor cortex, partially reversible via dopaminergic medication (Huang et al. 2006; Hanajima et al. 2007).

Neuropathological examinations in three individuals (death/autopsy time: 18, 39, and 90 years) showed no evidence of neurodegeneration but rather lower levels of dopamine, neuromelanine, tyrosine hydroxylase protein and striatum and/or substantia nigra activity (Rajput et al. 1994; Furukawa et al. 1999; Segawa et al. 2013). Histochemical analyses in DYT/PARK-GCH1 patients indicate typical decreases in neopterin and biopterin comparable to other monogenic DRD syndromes (Opladen et al. 2012).

Unfortunately, although the origin of the disease has been recognized for about 25 years, numerous individuals have a diagnostic and therapeutic delay, sometimes spanning decades (Trender-Gerhard et al. 2009), frequently causing lifelong impairment owing to iatrogenic treatment errors (Tadic et al. 2012). Clinical diagnosis is hampered by phenotypic variations (as described above), with unusual clinical presentations accompanied by spasticity (Wassenberg et al. 2020) or amyotrophy (Habibi et al. 2019).

In addition to dystonia, there is a rare autosomal-recessive variant of DRD caused by a biallelic GCH1 variant that has a more severe phenotype with hypotonia, oculogyric crises, and mental and motor developmental problems (Brüggemann 2012).Hyperphenylalaninemia was documented in these cases, but is unusual in autosomal-dominant DRD (Opladen et al. 2012). Pathogenic genetic variants in genes encoding other dopamine synthesis enzymes such as tyrosine hydroxylase (TH, OMIM # 605407), sepiapterin reductase (SR, OMIM # 612716) and 6-pyruvoyl tetrahydrobiopterine synthase (PTPS) are also associated with DRD as a complex dystonia syndrome with mental and motor development deficits and seizures (Chen 2020, Wijemanne 2015).

Dystonia-parkinsonism and other ATP1A3-related diseases

Rapid-onset dystonia-parkinsonism (RDP, DYT12, DYT/PARK-ATP1A3, OMIM # 128235) exhibits dystonic spasms advancing quickly within hours after inciting events (e.g., fever, birth, alcohol binge, falling, intense exercise, heat exposure, and psychological stress) (Brashear et al. 2007, 2018; Barbano et al. 2012). Mild dystonia affecting distal limbs may precede the first onset (Brashear et al. 2018). A rostrocaudal gradient of involvement is generally a trademark; bulbar symptoms of orofacial dystonia, dysarthria, pituitary gland and dysphagia are more severe than upper limb dystonia, and the latter are worse than leg symptoms (Brashear et al. 2007). In certain cases, hemidystonia without bulb involvement, paroxysmal dystonia, seizures and non-motor characteristics including cognitive impairment, mood problems, social anxiety and psychosis were documented (Pittock et al. 2000; Brashear et al. 2007, 2012, 2018; Barbano et al. 2012; Cook et al. 2014; Torres and Rosales 2017). Parkinsonism, especially bradykinesia and postural instability, occurs with dystonia. RDP generally occurs in youth and early adulthood, ranging from 4 to 58 years (Brashear et al. 2007, 2018; Rosewich et al. 2017).

Monoalellic genetic variation in the ATPase Na +/K + transmitting subunit alpha 3 (ATP1A3) gene is associated with RDP (de Carvalho Aguiar et al. 2004) and most cases of alternating childhood hemiplegia (AHC2, OMIM # 614820) (Heinzen et al. 2012; Rosewich et al. 2012; Ishii et al. 2013) and rare cerebellar ataxia syndrome, areflexia, pes cavus, optic atrophy, and s. (Demos et al. 2014). AHC has paroxysmal bouts of hemiplegia and dystonia with a rostrocaudal gradient and alternating laterality (usually before the age of 18 months), lasting minutes to weeks, and remission during sleep (Rosewich et al. 2017). Oculomotor abnormalities (e.g., monocular nystagmus and deviation), dystonic spasms, bulbar symptoms, dysautonomy, seizures, and respiratory abnormalities are other known paroxysmal events (Rosewich et al. 2014b), while non-paroxysmal features include developmental delay, dysarthria, ataxia, hypotonia, choreoathetosis, behavioral impairment, and less frequently pyramidal tract signs (Rosewich et al. 2014b, 2017). Meanwhile, CAPOS syndrome is defined by periods of ataxia, weakness, and encephalopathy following a febrile disease in infancy and youth, followed by symptom recovery, but then recurring (Demos et al. 2014; Brashear et al. 2018). The entire condition is infrequently encountered, with ataxia, isflexia, optic atrophy and sensorineural hearing loss being universal and pes cavus present only to a modest extent (Rosewich et al. 2017).

Previously, the three phenotypes associated with variation in ATP1A3 were thought to be distinct ally disorders, but with the identification of cases with combined features, the overlap of major signs and symptoms, and reports of SNVs causing both RDP and AHC, it is now increasingly recognized that RDP, AHC and CAPOS syndrome belong to a spectrum of ATP1A3-related disorders with RDP bein (Rosewich et al. 2017). Variation in ATP1A3 has recently been linked to three other rarer phenotypes: early childhood encephalopathic epilepsy (EIEE) (Paciorkowski et al. 2015; Marzin et al. 2018), recurrent encephalopathy with cerebellar ataxia (RECA) (Dard et al. 2015; Sabouraud et al. 2019), and rapid ataxia (ROA) (Sweadner

In all phenotypes, mutation in ATP1A3 is either inherited autosomally dominantly with partial penetration, or in most AHC instances as variations de novo (Rosewich et al. 2017). Asymptomatic carriers reported (de Carvalho Aguiar et al. 2004; Brashear et al. 2007, 2018).

To far, at least 137 pathogenic variants have been reported, consisting largely of missense SNVs and infrequently splice-altering variants, minor deletions, indels and major structural variations (HGMD database). Interestingly, polymorphisms linked with the RDP cluster in exons 8–17 and those linked with AHC in exons 17–18 (Rosewich et al. 2014b). C.1838C > T (RefSeq NM 152296.5) (p.Thr613Met) and c.2401G > A (p.Asp801Asn) replacements are recurrent variations producing RDP and AHC, while c.2452G > A (p.Glu818Lys) and c.974G > A (p.Gly325Asp) are only related to CAPOS syndrome (Demos et al. 2014; Lee et al. 2014). Some SNVs involve both RDP and AHC phenotypes (e.g. c.2600G > A, p.Gly867Asp; c.1109C > A, p.Thr370Asn; c.2767G > A, p.Asp923Asn; c.2267G > A, p.Arg756His; c.2401G > T, p.Asp801Gly) (Rosewich et al. 2014a; Viollet et al. 2015; Panagiotakaki et al. 2015; Holm et al. 2016). Recurrent c.2443G > A (p.Glu815Lys) SNV is linked with the most severe AHC phenotype with substantial intellectual impairment, motor impairment, seizures and epileptic state (Sasaki et al. 2014; Viollet et al. 2015; Panagiotakaki et al. 2015). Other unusual phenotypes include: c.2224G > T (p.Asp742Tyr) and c.2227 2229delGAC (p.Asp743del) in EIEE (Paciorkowski et al. 2015; Marzin et al. 2018), c.946G > A (p.Gly316Ser) in ROA (Sweadner et al. 2016), and c.2266C > T/c.2267G > A (p.Arg756Cys/p.Arg756His) in RECA (Dard et al. 2015; Sabouraud et al. 2019).

Variation in neurological-related ATP1A3. Variants were compiled from the HGMD database (hgmd.cf.ac.uk) and illustrated with regard to their position on the gene (exon), variant type (e.g., missense, nonsense, splicing, indel) and database frequency, with more commonly occurring variation depicted with bigger symbols. Variants were further categorised depending on the accompanying main phenotype (i.e. Rapid-onset Dystonia-Parkinsonism (RDP), Cerebellar Ataxia, Areflexia, Pes cavus, Optic atrophy, and CAPOS, Rapid-Onset Ataxia (ROA)/ataxia, Alternating Childhood Hemiplegia (AHC), or Epilepsy/Intellectual Disability). Exon-8 and exon-17 have the most variations, but the most common RDP-associated genetic mutation in exon-14 is c.1838C > T (p.Thr613Met).In AHC individuals, exon-17 and exon-18 variations cluster. Exon-18 is also the most prevalent variation linked with CAPOS syndrome (c.2452G > A, p.Glu818Lys).

The ATP1A3 gene codes for the [3] Na +/K +-ATPase subunit, a protein responsible for maintaining electrochemical gradient across neuronal cell membranes (de Carvalho Aguiar et al. 2004). AHC-associated substitutions are located in the protein's transmembrane and functional domains, leading to altered enzyme activity (Rosewich et al. 2014b; Holm et al. 2016). RDP-associated alteration causes lower protein expression or enzyme activity (Rosewich et al. 2014b). However, neither the location of the protein alteration nor the degree of pump expression and failure could explain differences in the clinical phenotype; genetic, epigenetic and environmental variables are therefore likely to have a role in etiology (Rosewich et al. 2014b; Lazarov et al. 2020). Neuropathological investigations in RDP revealed neuronal degeneration in globus pallidus, subthalamic nucleus, red nucleus and lower olive nuclei, cerebellum (Purkinje cell and granule cell layer) and subcortical white matter pathways; (Oblak et al. 2014). Interruption of the cerebellum and basal ganglia connections results in decreased motor control, as shown in an RDP pharmacological mice model where a sodium pump blocker was stereotaxically injected into the basal ganglia and cerebellum (Calderon et al. 2011).

Clinical characteristics of the RDP plateau about 30–60 days of illness initiation and afterwards continue without or modest improvement (Brashear et al. 2007; Rosewich et al. 2017). Rare reports of relief in lower limb symptoms, but not with the more severe bulb and upper limb symptoms (Brashear et al. 2018). A second bout of rapid exacerbation 1–9 years after patients started (Brashear et al. 2007). An unmet need remains the lack of a disease-modifying therapy and poor symptom management with L-dopa and other dopaminergic drugs. Flunarizine is used against acute episodes in AHC (Brashear et al. 2018). Pallidal stimulation was tested in four patients, with no three improvements and limited one improvement (Brücke et al. 2015). Regular surveillance, symptomatic dystonia and seizures, physiotherapy, speech therapy, psychotherapy (Brashear et al. 2018).

X-linked parkinsonism

XDP (DYT/PARK-TAF1, DYT3, OMIM # 314250) is an adult-onset, X-linked, neurodegenerative dystonia-parkinsonism. Most affected males undergo a phenotype transition from focal or segmental to generalized dystonia and eventually predominant parkinsonism as the disease progresses. However, Parkinsonian signs and symptoms have been described as co-occurring even at the onset with dystonia and may even be present in some cases (Evidente et al. 2002; Stephen et al. 2020). Dystonia, bulb involvement, and striatal toe are typically found (Song et al. 2020). Dystonic symptoms often occur in the craniocervical area and limbs, while parkinsonic symptoms are defined by axial stiffness, bradykinesia and postural instability (Pauly et al. 2020). Trembling in the limbs is an unusual parkinsonian symptom.

The illness occurs in people of Filipino heritage and is most prominent in Panay Island, Philippines, where the genetic founder is believed to have originated or established progeny (Fernandez and Rosales 2011; Domingo et al. 2015). This X-linked illness seldom occurs in females in whom the symptoms emerge later and on the parkinsonian side of the spectrum (Westenberger et al. 2013; Domingo et al. 2014). Most of the people affected suffer from severe symptoms through their working years and medical treatments remains restricted and symptomatic (De Roxas and Jamora 2019).

Pallidal stimulation results in a surprising rapid (and long-lasting) relief of dystonic symptoms, but may not be as efficient in treating parkinsonism (Brüggemann et al. 2019; Abejero et al. 2019).

As a neurodegenerative condition, XDP is characterized by basal ganglia neuropathological abnormalities. Studies in a small number of postmortem brains demonstrate neuronal loss in the striatum, with significant caudate head atrophy as a hallmark; (Goto et al. 2005, 2013). Caudate atrophy and sequential striatal degeneration are also the hallmarks of neuroimaging (Pasco et al. 2011; Hanssen et al. 2019); recent studies, however, reveal changes extending beyond basal ganglia and involving cortical structures (Brüggemann et al. 2016; Blood et al. 2018) as well as interference between basal ganglia and cerebellum (Hanssen et al. 2018). Nevertheless, the strong involvement of deeper motor nuclei is believed to be responsible for XDP movement disorder, neurophysiological alterations, and cognitive (i.e., executive control) abnormalities (Beste et al. 2017, 2018).

Using TMS, just one neurophysiological investigation has involved XDP patients. Unlike idiopathic, genetically undetermined individuals with dystonia or parkinsonism, XDP raised intracortical inhibition measurements (Weissbach et al. 2015b). These TMS paradigms are mediated mostly through the intracortical GABA–A dependent circuit of inhibitory interneurons in the motor cortex or premotor connections (Ziemann et al. 1996; Ilic et al. 2002). Therefore, it is logical to suppose that the increase in intracortical inhibition in XDP is not driven largely by the demise of an intracortical neuronal population, but rather by an imbalance in intracortical interneuronal populations due to uneven basal ganglia output.

In all XDP patients, the genetic etiology is linked to common genetic variations on X-chromosome in the TAF1 gene area (TATA box-binding protein-associated factor 1) (Nolte et al. 2003; Makino et al. 2007). Initial analyses discovered a single and homogenous haplotype constituted of non-coding mutations, considered refractory to recombination (Nolte et al. 2003; Domingo et al. 2015). Recent findings reveal that subhaplotypes have formed by recombining the original founder haplotype and that one of the disease-specific genetic alterations, a 2.6-kB SINE-VNTR-Alu-type (SVA) insertion, carries a polymorphic hexameric (CCCTCT) sequence that repeats within it (Bragg et al. 2017). The repeat size in this section ranges from 30 to 55 repetitions and is an important predictor of age at the beginning, probably explaining a fraction of variation in disease severity and phenotypic variability (Bragg et al. 2017; Westenberger et al. 2019). While the role of SVA insertion remains to be known, functional genomics investigations in cellular models suggest altered splicing and intron retention around insertion (Aneichyk et al. 2018).

Furthermore, removing insertion utilizing gene editing techniques resolves transcript changes and restores TAF1 expression (Aneichyk et al. 2018; Rakovic et al. 2018). All these lines of evidence include TAF1, and the insertion of SVA as the causal genetic factor in this illness. Notably, the changes in TAF1 expression in XDP are small, whether in stem cells or neural models, peripheral tissue or the few brain specimens studied, and are likely attributable to the tight control of the transcription factor (Makino et al. 2007; Ito et al. 2016; Domingo et al. 2016a; Rakovic et al. 2018). TAF1 is among the most restricted genes in the genome and the rare cases of loss of function coding variation described in humans result in an X-linked neurodevelopmental disorder with syndromic characteristics (OMIM: # 300966); some children have been described as having dystonia or other movement abnormalities (O'Rawe et al. 2015; Cheng et al. 2020).

Autosomal recessive dystonia-parkinsonism

Similar to XDP, DYT/PARK-PRKRA (DYT16; OMIM # 612067) was reported in geographic isolation (Camargos et al. 2008, 2012). Follow-up investigations in other groups discovered variation in the PRKRA (protein kinase, interferon-inducible double-stranded RNA-dependent activator) gene in other non-Brazilians with the typical phenotype of young-onset generalized dystonia combined with parkinsonism (Zech et al. 2014; Quadri et al. 2016). Yet internationally, DYT16 remains uncommon. DYT/PARK-PRKRA dystonia is often severe; symptoms may include sardonic grin, laryngeal involvement, and opisthotonus. Parkinsonian symptoms are modest, L-dopa-free, and may be absent.

PRKRA's initial illness-associated mutation is a homozygous c.665C > T (RefSeq NM 003690.5) (p.Pro222Leu) SNV co-segregated with illness in many families in southeastern central Brazil (Camargos et al. 2012). Non-Brazilian families (Polish, Italian) with young-onset dystonia-parkinsonism discovered the same variance and similar neighboring polymorphic genetic markers, indicating a shared founder. This SNV is lacking in gnomAD database homozygous state. Further screening on individuals with idiopathic dystonia demonstrated separate mutational events of the same locus (mutational hotspot vs. founder) and also enlarged the phenotypic to encompass dystonia without parkinsonian symptoms (dos Santos et al. 2018). Typically, DYT/PARK-PRKRA is inherited autosomally recessively; homozygous and compound heterozygous genetic variations were identified in patients and families with the disorder (de Carvalho Aguiar et al. 2015). The importance of the PRKRA variant in phenotypically compatible instances is still uncertain. Patient cells with p.Pro222Leu protein substitution had an altered reticulum stress response defined by delayed eIF2-alpha phosphorylation, a biochemical pathway similarly identified in DYT-TOR1A (Vaughn et al. 2015; Rittiner et al. 2016).

Other dystonia-parkinsonism causes

Other genetic conditions that may occur with dystonia-parkinsonism include Wilson's disease (OMIM # 277900, ATP7B) and other metal metabolism disorders, including neurodegeneration with brain iron accumulation syndromes (OMIM # 234200, PANK2; OMIM # 610217, PLA2G6; OMIM # 606693, Kufor-Rakeb disease, ATP13A2; and others) and manganese transport disorders (OMIM # 613280, PLA2G6; OMIM # 6066693, ATP13A2). The dystonic and parkinsonic symptoms in these conditions are exceedingly diverse and often coincide with additional signs of metal buildup in the brain or other organs. Huntington's disease, especially the juvenile form, and different spinocerebellar ataxias with dystonia and parkinsonism (Fusilli et al. 2018; Klockgether et al. 2019). Parkinsonism may also be characteristics present in paroxysmal/nonpersistent illnesses, i.e. kinesigenic (OMIM # 128200, PRRT2; OMIM # 601042, SLC2A1) and non-kinesigenic dystonias (OMIM # 118800, PNKD). Dystonia-parkinsonism can also be present in H-ABC (hypomyelination with basal ganglia and cerebellar atrophy) syndrome (OMIM # 128101, TUBB4A), a complex dystonia with pyramidal indications and symptoms and specific white matter MRI abnormalities.

Myoclonal dystonia

SGCE-associated myoclonus-dystonia MYC/DYT-SGCE (DYT11, OMIM # 159900) commonly begins with widespread myoclonic jerks that occur mostly in the neck and proximal upper limbs in the first and uncommon decades of life. Dystonia is less apparent in most individuals than myoclonus and remains isolated to the upper half of the body, with cervical dystonia and writing cramp being the most prevalent dystonic signs (Nardocci et al. 2008; Nardocci 2011). Isolated myoclonus without dystonia, previously known as essential myoclonus, also occurs. Many individuals suffer from mental comorbidities, including anxiety, depression, dependence on alcohol and obsessive-compulsive disorders (Peall et al. 2011; Weissbach et al. 2013; Timmers et al. 2019). Interestingly, patients report an increase in somatic symptoms under psychological stress and a considerable decrease in alcoholic myoclonic jerks (Hess et al. 2007), which might be objectivated in a clinical and neurophysiological investigation (Weissbach et al. 2017).

To far, more than 70 pathogenic mutations of the epsilon sarcoglycan (SGCE) gene have been found with myoclonus dystonia (Asmus et al. 2007; Grünewald et al. 2008). Epsilon-sarcoglycan is a transmembrane protein that forms part of the dystrophin-glycoprotein complex, therefore having crucial implications for cytoskeletal maintenance and cell transport processes (Esapa et al. 2007). SGCE occurs in several brain areas, including the cerebellum, and appears to have a function in synaptic signal transduction (Nishiyama et al. 2004; Ritz et al. 2011; Xiao et al. 2017).

Neurophysiologically, individuals with MYC/DYT-SGCE have reduced motor learning, greatly improving alcohol intake (Weissbach et al. 2017). Recently, a shift in the visual sensory processing of the temporal discrimination threshold, linked with myoclonal severity and anatomical abnormalities in the primary visual cortex, was observed (Tarrano et al. 2020). Structural (van der Meer et al. 2012), functional (Beukers et al. 2011) and metabolic imaging investigations (Carbon et al. 2013) also reveal subcortic motor symptoms.

Currently, pharmacological treatment does not satisfy all symptoms of myoclonal dystonia. Anticholinergics (Raymond et al. 2020), benzodiazepines (Raymond et al. 2020), zonisamide (Hainque et al. 2016), high doses of L-dopa (Luciano et al. 2009), sodium oxybate (Frucht et al. 2005), and antiepileptic drugs (Raymond et al. 2020) show variable results and several side effects that limit treatment. With deep brain stimulation of globus pallidus internus or thalamus, movement problems might be significantly improved (Rughani and Lozano 2013; Wang and Yu 2020; Besa Lehmann et al. 2020).

MYC/DYT-SGCE is transmitted in an autosomal dominant form with limited penetration and maternal imprinting (Grünewald et al. 2008), an epigenetic DNA alteration in which maternal allele methylation inhibits SGCE gene expression. Thus, in most myoclonus dystonia families, the condition only develops if the father inherits the pathogenic allele. Preferential paternal allele expression was maintained in cortical neurons produced from pluripotent stem cells (Grütz et al. 2017) produced from SGCE genetic variant carriers, demonstrating consistency in human gene regulation mechanism and this disease-in-a-dish paradigm.

Other genes of myoclonus-dystonia

Variations were also related to myoclonus dystonia in four other genes, namely KCDT17 (Mencacci et al. 2015b), CACNA1B (Groen et al. 2015a), KCNN2 (Balint et al. 2020) and RELN (Groen et al. 2015b), with KCTD17 being the only gene replicated in additional research (Graziola et al. 2019; Marce-Grau et al. 2019). In example, the potential genetic mutation in CACNA1B was detected at unusually high frequency in controls and population databases, disputing the link of this gene with illness (Mencacci et al. 2015a; Domingo et al. 2016b). MYC/DYT-specific KCDT17's phenotype comprises modest myoclonic symptoms in addition to progressive, widespread dystonia involving oromandibular and laryngeal muscles (Mencacci et al. 2015b; Graziola et al. 2019; Marce-Grau et al. 2019). Variation in anoctamine 3 (ANO3), related to solitary dystonia with craniocervical and upper limb-predominant symptoms, was also reported in instances of myoclonus dystonia in infancy (< 5 years) (Yoo et al. 2018; Tunc et al. 2019; Delamarre et al. 2019).

Conclusion

From the foregoing, one may infer that the combined dystonia syndromes are diverse and that even the illness phenotypes induced by the same gene are widely varied. There are beginning age ranges, symptom presentation variances, varying disease manifestations, and unusual presentations. In addition, accepting clinical exome sequencing and gene panels in genetic disease diagnosis has broadened genotypes and phenotypes. It is crucial to keep abreast of the breakthroughs in genetic technology and to understand the whole spectrum of these interesting illnesses. Online resources are regularly updated, integrating genetic and phenotypic information. Neurophysiology and imaging approaches complement clinical results and are vital for improved phenotyping. Recent investigations hint at possible abnormal interaction between MYC/DYT-SGCE, XDP, and RDP basal ganglia-cerebellar and brainstem-cerebellar circuits. Identifying links between network disruptions and cellular malfunction will enhance our understanding of the underlying pathophysiology and teach new therapeutic techniques.

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