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Review article

GNAO1-related movement disorder: An update on phenomenology, clinical course, and response to treatments

Maria Novelli [a], Serena Galosi [a,*], Giovanna Zorzi [b], Simone Martinelli [c], Alessandro Capuano [d], Francesca Nardecchia [a], Tiziana Granata [b], Luca Pollini [a], Martina Di Rocco [a,c], Carlo Efisio Marras [d], Nardo Nardocci [b], Vincenzo Leuzzi [a]

[a] Department of Human Neuroscience, Sapienza University of Rome, Italy
[b] Department of Pediatric Neuroscience, IRCCS Foundation Carlo Besta Neurological Institute, Milan, Italy
[c] Department of Oncology and Molecular Medicine, Istituto Superiore di Sanità, Rome, Italy
[d] Department of Neuroscience, Bambino Gesù Children Hospital, Rome, Italy

A B S T R A C T

Aim: To evaluate clinical phenotype and molecular findings of 157 cases with *GNAO1* pathogenic or likely pathogenic variants delineating the clinical spectrum, course, and response to treatments.
Method: Clinical phenotype, genetic data, and pharmacological and surgical treatment history of 11 novel cases and 146 previously published patients were analyzed.
Results: Complex hyperkinetic movement disorder (MD) characterizes 88% of *GNAO1* patients. Severe hypotonia and prominent disturbance of postural control seem to be hallmarks in the early stages preceding the hyperkinetic MD. In a subgroup of patients, paroxysmal exacerbations became so severe as to require admission to intensive care units (ICU). Almost all patients had a good response to deep brain stimulation (DBS). Milder phenotypes with late-onset focal/segmental dystonia, mild to moderate intellectual disability, and other minor neurological signs (i.e., parkinsonism and myoclonus) are emerging. MRI, previously considered noncontributory to a diagnosis, can show recurrent findings (i.e., cerebral atrophy, myelination and/or basal ganglia abnormalities). Fifty-eight *GNAO1* pathogenic variants, including missense changes and a few recurrent splice site defects, have been reported. Substitutions at residues Gly^{203}, Arg^{209} and Glu^{246}, together with the intronic c.724-8G > A change, account for more than 50% of cases.
Interpretation: Infantile or childhood-onset complex hyperkinetic MD (chorea and/or dystonia) with or without paroxysmal exacerbations, associated hypotonia, and developmental disorders should prompt research for *GNAO1* mutations. DBS effectively controls and prevents severe exacerbations and should be considered early in patients with specific GNAO1 variants and refractory MD. Prospective and natural history studies are necessary to define genotype-phenotype correlations further and clarify neurological outcomes.

1. Introduction

GNAO1, together with *ADCY5, GNB1, PDE10A, PDE2A, GPR88, HPCA*, and *GNAL*, is part of an emerging group of genes encoding proteins involved in postsynaptic dopaminergic signaling [1]. These proteins play a fundamental role in controlling signaling through G-protein-coupled receptors (GPCRs) and the cyclic adenosine monophosphate (cAMP) cascade, a critical pathway involved in post-synaptic brain connectivity modulation with a crucial role at the level of basal ganglia [2–4].

Gαo, the product of *GNAO1,* is one of the most abundant proteins in the brain [5], with an extremely complex and mostly unknown network of interactions. Recently discovered functions of Gαo concern striatal medium spiny neurons (MSNs) circuitries of both the direct (dMSN) and indirect (iMSN) pathways [6,7].

Dominant *GNAO1* variants were first described in 2013 by Nakamura and colleagues in patients with early infantile-onset epileptic encephalopathy (EIEE17) (MIM#615473) [8]. A different phenotype was later identified, characterized by severe developmental delay and early onset disabling movement disorder (MD) either with Developmental Epileptic Encephalopathy or without seizures (NEDIM) (MIM#617493) [9,10]. In the last few years, further cases with "atypical" presentations as well as milder phenotypes and/or late-onset neurological impairment have been reported.

MD, reported in almost all patients, includes chorea, dystonia, orofacial dyskinesia, complex motor stereotypies and is typically described as fluctuating and hyperkinetic [4].

The emergence of triggered dystonic–dyskinetic status marks the

* Corresponding author. Unit of Child Neurology and Psychiatry, Department of Human Neuroscience, Sapienza University of Rome, Via dei Sabelli 108, 00185, Rome, Italy.
E-mail address: serena.galosi@uniroma1.it (S. Galosi).

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evolution of a relevant number of patients leading possibly to life-threatening conditions caused by severe and long-lasting exacerbation of MD [7].

However, hypokinetic phenotypes characterized by hypo and bradykinesia, other neurological signs (i.e., tremor, oculogyric crisis, spasticity, etc.), and profound postural development impairment were also reported.

Pathogenic mechanisms underlying *GNAO1* mutations remain largely unexplained and the original distinction between gain- and loss-of-function mutations, based on their ability to suppress cAMP production, does not fully account for the clinical and functional abnormalities related to *GNAO1*. Recent works suggest that all *GNAO1* variants can disrupt GPCR signaling through loss-of-function (LOF) mechanisms and dominant-negative interferences, which are not mutually exclusive [6].

In this case series and literature review, we provided an overview of the main clinical and genetic characteristics of all individuals with *GNAO1*-related disorders that have been published to date, including 11 new personal cases. We intend to characterize the MD phenomenology better in the clinical course, including precipitating triggers provoking dyskinetic status and the best available therapeutic approaches for this condition.

2. Materials and methods

2.1. Personal cases

2.1.1. Clinical data

Eleven new genetically proven patients with *GNAO1*-related disease were recruited at the Department of Pediatric Neuroscience of IRCCS Foundation Carlo Besta Neurological Institute (Milan-Italy), Department of Human Neuroscience, Sapienza University of Rome (Italy), and Bambino Gesù Children Hospital, Rome (Italy).

We collected clinical history and evolution information focusing on MD phenomenology and response to pharmacological and surgical treatment. The following data were systematically collected: mutation, sex, current age, age at the onset, clinical phenotype, initial symptoms, presence and type of MD, MD exacerbations, triggers, concomitant epilepsy, developmental/cognitive outcome, and therapeutic approaches (extended data are available as Supplementary materials). All patients were clinically evaluated and underwent neurological examinations, brain MRI (except patient 8), and other routine studies (EEG, blood chemistry tests).

In addition to the new cases, we provided updated clinical data of 5 previously reported cases followed up in our centers [10–12].

Finally, based on longitudinal videos from our series (11 new and 5 previously published patients), we could better characterize MD phenomenology and delineate the different steps of the motor derangement emergence and progression observed in this condition.

2.1.2. Genetic data

The diagnosis was addressed by Next Generation Sequencing (NGS) panels or whole exome sequencing (WES). All the identified variants were confirmed by Sanger sequencing.

2.1.3. DBS

Globus pallidus internus (GPi) DBS and/or pallidotomy were performed due to severe untreatable generalized, hyperkinetic MD. Evolution and post-surgical outcome were assessed in all patients after surgery. Details about interventions performed and complications were noted. Stimulation parameters were recorded, when available, at the time of the initiation of stimulation and the last follow-up.

Surgery was performed at the IRCCS Foundation Carlo Besta Neurological Institute (Milan, Italy) and Bambino Gesù Children Hospital (Rome, Italy). Regarding the DBS group, all patients underwent bilateral, frame-based stereotactic implantation of DBS electrodes into the GPi and connected to an implantable neurostimulator in the subclavian/periumbilical region. Confirmation of electrode placement was obtained via an immediate postoperative MRI scan.

2.2. Review of literature

A literature review, including papers published up to June 2022, was performed. Searches were made using PubMed and Google Scholar, employing the following keywords: “GNAO1”, “GNAO1” plus “movement disorder”, “GNAO1” plus “epilepsy” and “GNAO1” plus “DBS”.

All the reports, including patients harboring a molecularly confirmed *GNAO1* variant and clinical details, were collected. We selected English and non-English-written articles. Ten patients described in 7 articles reported without a detailed delineation of their clinical picture or definite genetic diagnosis were excluded. Altogether, 52 articles were extracted from the literature search, describing 146 patients. We reviewed all cases with *GNAO1* pathogenic or likely pathogenic variants according to American College of Medical Genetics and Genomics (ACMG) criteria, focusing on their clinical phenotype, especially in relation to MD phenomenology, clinical course, and treatment. In detail, we collected data about mutation, sex, current age, age at the onset, clinical phenotype, initial symptoms, presence and type of MD, MD exacerbations, triggers, concomitant epilepsy, and treatment (drugs, surgery).

Videos from eight of our eleven cases and published cases (31 patients) were collected and analyzed by pediatric MD specialists to better characterize the patterns of MD emergence and outcome. Finally, our data were critically discussed and compared with those inferred from the literature.

2.3. Genetics

GNAO1 pathogenic/likely pathogenic variants were reviewed according to the ClinVar database and ACGM classification.

2.4. Statistics

Descriptive statistics were performed and presented as percentages for qualitative variables.

3. Results

3.1. Clinical description: personal cases and literature review

3.1.1. GNAO1 cohort: epidemiology and clinical background

Through the literature search, 52 articles were collected, describing 146 patients with pathogenic/likely pathogenic *GNAO1* variants between 2013 and 2022. In addition, we included 11 unpublished cases detected in our centers. Our cohort, therefore, includes 157 patients (89 females, 67 males, 1 not reported) (Table 1).

The mean age at publication was 11 y (range 1–66 y). When considering the diagnosis at the time of publication, most patients (56.0%) showed isolated MD, 51 patients (32.4%) suffered from a complex phenotype including both MD and epilepsy, 15 (9.6%) experienced isolated epilepsy, and 3 (1.9%) had an unspecified neurodevelopmental disorder and/or other phenotypes.

In almost all cases, symptoms appeared within the first year of life, with central hypotonia and developmental delay representing the main neurological alterations at the initial stage.

Trunk hypotonia, with delayed or no emergence of associated postural reactions, is reported in 115 (73.2%) patients, while developmental delay is reported in 88.5% of cases (139 patients), resulting in motor and language disability in the following decades. Marked speech and language impairment and intellectual disability, though in the presence of relatively spared understanding and interactive skills, were largely observed. Few and selected cases, which will be discussed below, differ from this pattern.

Table 1
Frequency of clinical characteristics of all GNAO1 patients.

GNAO1 patients N = 157 (%)	
Sex	
Female	89/157 (56.68%)
Male	67/157 (42.67%)
Mean age (last follow-up) [mean ± SD]	11 y (±1–66 y)
Developmental delay	139/157 (88.5%)
Hypotonia	115/157(73.2%)
Movement Disorder	139/157 (88.5%)
Age at MD onset [mean]	51 months
Dystonia	107/157 (68.2%)
Chorea	68/157 (43.3%)
Dyskinesia	56/157 (36.6%)
Parkinsonism	20/157 (12.73%)
Ocular abnormalities	10/157 (6.36%)
Periodic exacerbations	62/157 (39.5%)
Status dystonicus - need for ICU	46/157 (29.29%)
Surgery	35/157 (22.29%)
Epilepsy	75/157 (47.77%)
Feeding difficulties	44/157 (28.0%)
Dysmorphic features	16/157 (10.2%)
Neuroimaging abnormalities	62/157 (39.49%)
Cortical atrophy	40/157 (25.47%)
White matter abnormalities	21/157 (13.37%)
Basal ganglia abnormalities	15/157 (9.55%)
Follow up data: deceased patients	14/157 (8.9%)

Feeding difficulties were reported in 44 patients (28.0%) and required gastric tube placement in 21.

Dysmorphic features were rarely reported, whereas microcephaly was relatively common in our and previously reported cohorts (16 cases, 10.2%) [13–15]. By reviewing videos and images of reported patients [10] and our series, we observed that a wide forehead was a frequent facial feature.

Other medical issues, such as kidney and ocular abnormalities, and psychiatric disorders (i.e., Attention deficit hyperactivity disorder, Obsessive compulsive disorder, anxiety) have rarely been reported (patient 7 of our series and other literature patients) [12,14]. Equally, autonomic disturbances, such as altered thermoregulation and sweating were also described, with a high presentation rate during MD exacerbations. Cardiac dysfunction, in the form of altered heart rhythm, may be underrecognized and deserve further investigations in future studies [16].

To date, global *GNAO1* mortality is relevant, with 14 (8.9%) patients dying because of different complications of their neurological disorder, including MD exacerbations, respiratory failure, and neurological deterioration. One patient previously included in the series reported by Schirinzi et al. (case 1) died during follow-up, after 6 years from pallidotomy during an intercurrent illness, with no clear explanation or occurrence of MD exacerbation at the time of death [11].

Regarding MRI studies, nearly half of the patients had normal brain neuroimaging, while the others presented variable MRI abnormalities ranging from cerebral atrophy (often described as progressive and diffuse) which is the most relevant finding, to myelination disorders (i.e. hypomyelination, delayed myelination), basal ganglia abnormalities (i.e. T2w-hypointense signal changes in the GP, hypoplasia or atrophy of caudate nucleus) and corpus callosum defects (thin corpus callosum) (percentages in Table 1).

Most of our patients underwent several neuroimaging studies over time (mean age at the last evaluation was 8). Cases 4, 6, 7, 9, 11 had normal MRI, while cases 2, 5 showed signs of atrophy (respectively, progressive supratentorial brain atrophy prevalent in the frontal regions and diffuse supratentorial atrophy and cerebellar atrophy). Case 10 showed altered signals in basal ganglia. Cases 3 and 6 showed delayed myelination. Case 1 had a combination of these abnormalities, and thin corpus callosum (details in supplementary file).

3.1.1.1. Movement disorder phenotype and course. *GNAO1*-related MD usually starts during infancy or childhood, with a mean age at onset (available for 101 patients) of 51 months (median 26 months) and wide variability (range from 1 month to 47 years).

MD is predominantly hyperkinetic and characterized by fluctuating and often combined dystonia, chorea, athetosis, dyskinesia and ballism. The abnormal movements in *GNAO1* patients typically appear as sudden and violent jerky involuntary movements affecting the limbs, neck, and oromandibular district. Paroxysmal twitches and writhing movements are also reported with violent dystonic postures of the trunk up to the opisthotonus.

Dystonia was the most reported sign (107 patients, 68.2%), usually described as generalized and associated with other MDs or neurological disturbances in 73/107. A progression from limb to generalized dystonia was observed in almost all our personal and several literature cases [10,17,18].

Some recently reported mild "atypical" phenotypes showed segmental or multifocal slowly progressive dystonia without chorea and paroxysmal exacerbations, sometimes associated with intellectual disability and other minor neurological signs [12,18,19]. However, the latter seems to be a rarer presentation than the classic form with early-onset severe paroxysmal MD.

Chorea is reported in 68 (43.3%) patients and is often described as mixed choreoathetoid and/or ballistic MD. Prominent orofacial dyskinesia and dystonia, involuntary repetitive movements of the mouth and face negatively affecting the ability to feed were also widely reported and clearly described in 26 patients [14,20].

Pyramidal features (ankle clonus, hyperreflexia, Babinski sign) were also observed in association with dystonia.

Parkinsonian features (i.e resting tremor, bradykinesia, reduced movements) [13,14] and ocular movement abnormalities (i.e saccades alterations, nystagmus, oculogyric crisis, downward gaze palsy, and fixation deficit with head nodding) are increasingly recognized, observed in 5 of our patients and in multiple literature cases [7,10,11,21].

MD fluctuations with evidence of periodic exacerbation of hyperkinetic and involuntary movements widely characterize patients (62 cases, 39.5%), and led to dystonic–dyskinetic status (SD) requiring multiple intensive treatments in 46 of them (see Supplementary Materials for detailed clinical histories of the new patients). SD is constantly associated with significant medical morbidities. Although data on ICU admission are lacking, hyperthermia (described in 9 patients) and elevated creatine kinase levels (described in 24 patients) are the most frequent abnormalities. Fractures and sepsis are also described. Data about comorbidities management and duration of ICU stay are mostly missing.

The age at first exacerbation has a wide range, from 1 to 17 years (data largely incomplete). Reported triggers for MD exacerbations included positive and negative emotions, pain, infections, fever, intercurrent illnesses, high external temperature, dehydration, surgery, change of positioning, intention to move, exercise, and menstruation [10,21]. Considering the entire cohort, data about the age at MD presentation and age at first MD exacerbation were available for 75/157 (<2 years of age in 47 patients and >2 in 28) and 34/157 patients, respectively. We observed that 76% (36/47) of patients with MD onset before 2 years of age had severe exacerbations, while it happened for only 21% (6/28) of patients with MD onset after 2 years of age.

Based on these retrospective data it is not possible to draw any conclusion about the relationship between the age of onset of MD or severe paroxysmal exacerbations and the clinical outcome. However, patients tend to manifest different MD onset patterns, course, timing, and severity of exacerbations in a continuum of overlapping manifestations and phenotypes.

Many patients initially show severe central hypotonia, and delayed neuromotor development from early stages [10,21,22]. Choreo-dystonic MD may also be observed from the first months of life.

Reviewing presymptomatic home videos from our patients (patients

6,8,11 and one patient also reported by Danti and colleagues [10]), we noticed that at this initial stage the child may still show a normal pattern of object reaching and handling and the ability to explore the object by passing it from one hand to the other, as well as to maintain visual attention to the ongoing activity (video available in Danti et al., 2017) [10]. However, in the following stage of the disease (usually during the second year of life in our subjects), dystonic postures of limbs and progressive vanishing of the intentional initiative of upper limbs become evident. In a few months, facial mimic wains, and a generalized loss of motor initiative (hypokinesia) may also occur.

However, as confirmed by literature and personal cases, in most patients choreic/dystonic movements progressively become pervasive and generalized, often becoming drug-resistant and highly interfering with daily activities. In this context, frequent paroxysmal dystonic-dyskinetic attacks and progressive course characterize the clinical evolution of these children from the earliest years of life, leading to life-threatening conditions and recurrent ICU admissions [23,24].

Some patients, such as our case 4 and other previously reported patients [11,21], may manifest an initially more benign course with better postural achievements (can be ambulant), less severe neurodevelopmental disorder, with or without chorea, resembling dyskinetic cerebral palsy. Later in life, similarly to others, they may develop a sudden and unexpected severe dyskinetic exacerbation, which often precedes the onset of a prominent chronic choreic MD and motor deterioration with subsequent dystonic and/or spastic tetraparesis.

Finally, *GNAO1* patients with mild phenotypes are increasingly recognized. Late-onset dystonia (after 2 years of age), dysarthria, gait abnormalities, mild to moderate ID or normal cognitive functioning are reported in these patients, while severe encephalopathy seems missing [12,18,19,25,26]. Choreoathetosis and MD exacerbations are rare. The single nucleotide variant c.724-8G > A appears to be highly associated with this new phenotype.

3.1.1.2. Epilepsy. Sixty-six reported patients (42.3%) had epilepsy, ranging from severe early onset forms with infantile spasms, tonic seizures, epilepsy of infancy with migrating focal seizures to late-onset milder generalized and/or focal epilepsies. Among our 6 patients suffering from epilepsy, the first episode occurred in the neonatal-infantile period in 3 patients and during childhood in 2 patients. Our patients variably presented with generalized, focal, or combined epilepsy. Two of them presented generalized epilepsy and an episode of status epilepticus (pt. 1 and 2). Except for these two cases, epilepsy was well-controlled and not particularly disabling in our patients.

From the literature and personal cases review, the c.607G > A (p. Gly203Arg) variant appears frequently associated with early-onset and drug-resistant epilepsy, accompanied by MD. All 15 patients carrying this pathogenic variant developed early onset epilepsy, with 11/15 having neonatal epilepsy and 8/15 being drug-resistant.

Table 2
Clinical and demographic features of unreported GNAO1 patients.

Pt ID	GNAO1 mutation	sex	Age (y)	Symptoms onset and age	onset/type MD	MD exacerbations	Drugs for MD (and efficacy)	DBS (age -y)	Epilepsy	medical issues (+ autonomic dysfunction	MRI
1	c.607G > A; p. Gly203Arg	F	7	6 m	dystonia, chorea, dyskinesia	yes	NTZ, TBZ(+)	-	partial status epilepticus in fever (1 y), then tonic seizures	microcephaly, sweating	global atrophy (progressive)
2	c.607G > A; p. Gly203Arg	F	27	2–3 m	dystonia, chorea, dyskinesia	yes (from 9 y recurrent SD requiring ICU)	ITB pump,THP, TBZ, CZP	yes (9)	infantile spasms, focal seizures, one focal epileptic status	growth deficit, optic atrophy, tubulopathy, marked salivation	global atrophy
3	c.625C > T; p. Arg209Cys	M	11	1 m	dystonia, chorea, dyskinesia	no	–	–	focal and generalized seizures	microcephaly	white matter abnormalities
4	c.625C > T; p. Arg209Cys	F	17	1 y	dystonia, chorea, dyskinesia	yes (recurrent SD from 11 y, requiring ICU)	Botulinum, THP, CZP, BAC, GPN (+), CLO	yes (15)	focal seizures	venous thrombosis	normal
5	c.626G > A; p. Arg209His	F	11	1 y	dystonia, chorea, dyskinesia	yes	THP, BAC, TBZ, CLO, benzodiazepines	yes (7)	no	no	global atrophy (progressive)
6	c.723+1G > A	M	3	1 m	dystonia, chorea, dyskinesia	yes (from 24 mo) not severe	THP (not benefit), TBZ	-	no	no	hypomyelination
7	c.724-8G > A	M	20	infancy	dystonia, chorea, dyskinesia	no	MPH (+), THP (+), l-dopa, Amantadine	-	no	ADHD, mild temporal peripapillary atrophy	normal
8	c.736G > A; p. Glu246Lys	F	4	8 m	dystonia, chorea, dyskinesia	yes	THP, TBZ	-	no	–	–
9	c.736G > A; p. Glu246Lys	F	17	3 m	dystonia, chorea, dyskinesia	yes (from 12 y)	TBZ, diazepam, LEV, l-dopa, CZP, BAC,	-	no	microcephaly, sweating and flushing	normal
10	c.736G > A; p. Glu246Lys	M	13	1 m	dystonia, chorea, dyskinesia	yes (from 8 y)	THP, benserazide, CLB (+), CZP(+) TBZ(+)	-	febrile seizures; generalized tonic seizures in sleep	neonatal jaundice, deafness	altered signal (basal ganglia)
11	c.736G > A; p. Glu246Lys	M	5	1 m	dystonia, chorea, dyskinesia	no	–	-	focal seizures	–	normal

*TBZ tetrabenazine, CZP Clonazepam, THP Trihexyphenidyl, CLB Clobazam, BAC Baclofen, LEV Levetiracetam, NTZ Nitrazepam, MPH Methylphenidate, GPN Gabapentin, CLO Clonidine.

On the other hand, 8 out of the 14 children with the c.625C > T (p. Arg209Cys) variant manifested infantile/childhood onset of seizures and a good response to treatment.

3.1.2. Molecular spectrum of GNAO1 pathogenic variants

According to ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) and available literature, 50 pathogenic and 37 likely pathogenic variants have been reported so far. Among these, fifty-eight changes have been identified in the present cohort of 157 previously published and newly identified patients (Table S1). Most of them are missense mutations affecting highly conserved residues spread across the length of the protein. Other variants include a few putative splice site defects and, rarely, inframe deletions (Table S1) [10,11,27,28]. Twelve variants recur in at least three unrelated subjects.

We identified six previously reported variants in the new cohort of 11 patients, including four missense changes and two intronic substitutions affecting transcript processing (see Table 2). All changes were shown to occur as *de novo* events.

Considering the entire cohort of patients, codons 203, 209 and 246 emerge as mutational hotspots. Gly^{203} is located near the GTP-binding pocket of Gαo, whereas Arg^{209} and Glu^{246} are implicated in forming a salt bridge playing a key role in adopting the active conformation of the protein [29]. Missense mutations at these residues (*i.e.*, p.Gly203Arg, p. Arg209Cys/His/Gly/Leu, and p.Glu246Lys/Val/Gly) account for 40.1% of total cases (Table S1). All these variants appear to be highly associated with severe MD exacerbations, suggesting the need for more intensive and timely treatment in a subcategory of *GNAO1*-affected patients. Finally, the c.724-8G > A intronic variant has recently been described in an increasing number of patients (11.5%) with progressive dystonia without exacerbations. This change was shown to cause abnormal splicing leading to the insertion of two novel amino acids (p. Thr241_Asn242insProGln) [30]. A subset of pathogenic variants, including two putative loss-of-function changes leading to *GNAO1* haploinsufficiency, has recently been reported in patients with relatively mild clinical features, mainly late-onset dystonia, further expanding the spectrum of *GNAO1*-related phenotypes [18]. This finding supports the notion that simple loss-of-function variants with no dominant-negative or neomorphic activity (i.e., haploinsufficiency) are not associated with the canonical presentation of EIEE17 or NEDIM, or with severe mixed phenotypes.

3.1.3. Management

3.1.3.1. Pharmacological treatment. Considering largely incomplete data, about 2/3 of patients (83 patients) required pharmacological treatment for their MD.

Tetrabenazine, followed by Trihexyphenidyl and Benzodiazepines, were the most used drugs/class of drugs, usually as a polytherapy to obtain better control of motor symptoms [7,10,31]. Sporadic cases of response to other drugs, such as Risperidone [13] Gabapentin [32], Topiramate [33] and Levetiracetam [28], have been reported (**Table 3**). When considering personal cases, MD was often severe, and treatment was required for all but one patient (pt. 11). In 4, good/fair symptom control was achieved with monotherapy. The remaining six required higher doses and multiple pharmacological treatments (4–7 drugs). Benzodiazepines, trihexyphenidyl, baclofen, clonidine, and others were employed, with the most used being tetrabenazine (6/11), with evidence of some clinical benefit in all of them. Responsiveness to medical treatment was evaluated over time through clinical observations and video recordings.

3.1.3.2. DBS. A total of 35 patients underwent surgical treatment (3 novel cases, 32 cases from literature). Among patients who had surgery, 32 underwent GPi DBS, 1 was treated with pallidotomy, 1 underwent pallidotomy as the third surgery after GPi and subthalamic nucleus (STN) DBS, and 1 STN DBS.

Table 3
Effective pharmacological treatments for *GNAO1*-related movement disorders.

Drug	Dosage	Efficacy	Genotype
Tetrabenazine	1-10, 5 mg/kg/day up to 300 mg/day	Improvement of baseline dyskinetic movement less effective on choreic storm	c.139A > G; p. Ser47Gly [10] c.737G > A; p. Glu246Gly [31] c.626G > A; p. Arg209His [28] c.709G > A; p. Glu237Lys [7] c.736G > A; p. Glu246Lys [7] c.736G > A; p. Glu246Lys [13]
Risperidone	1/1,5 mg/day	Improvement of baseline dyskinetic movements	c.736G > A; p. Glu246Lys [13] c.626G > A; p. Arg209His [13]
Gabapentin	up to 40 mg/kg/day	Relevant improvement of dyskinetic movements	c.626G > A; p. Arg209Cys [32]
Topiramate	7,5 mg/kg	Frequency of chorea decreased dramatically, with reduced need for benzodiazepines	c.625C > T; p. Arg209Cys [33]
Levetiracetam	NA	Improvement of baseline dyskinetic movements	c.709G > A; p. Glu237Lys [28]
Diazepam	up to 40 mg x3 (oral)	Effective on MD exacerbations	c.736G > A; p. Glu246Lys [13]
Phenobarbitone	6–16 mg/kg/d	Helpful in association with Tetrabenazine/rescue therapy	c.709G > A; p. Glu237Lys [7] c.736G > A; p. Glu246Lys [7]
l-Dopa	up to 400 mg/day	Mild/subjective improvement of dystonia	c.68T > C; p. Leu23Pro [18] c.644G > A; p. Cys215Tyr [18] c.724-8G > A [18] c.725A > C; p. Asn242Thr [18]

In our patients, stimulation settings were adjusted based on the clinical response and the possible occurrence of undesirable effects. The final parameters were reached gradually over time (Table 4).

Not all patients had detailed information on pre-surgical and post-operative periods, however; all subjects were unresponsive to multiple pharmacological treatments. Most of them were implanted due to severe choreoathetosis and frequent MD exacerbations, although recent works support the use of GPi DBS also in *GNAO1* patients with severe disabling dystonia in the absence of paroxysms [18].

The mean age at the time of surgery was 10 (range 4–17 y). Regarding surgery indications, 17 patients required intervention for the onset of a refractory dystonic-dyskinetic state in the acute phase, while 12 were implanted in an election due to MD exacerbations recurrence or severe dystonia (6 NA).

DBS successfully interrupted dystonic-dyskinetic state in 16/17 patients, allowing weaning from sedation and extubation or discharge from ICU, resulting in life-saving and effective intervention. One of our cases (case 2) required GPi and STN DBS, followed by pallidotomy because of the persistence of SD, with the final benefit from ablative surgery. The reasons for DBS failure in this patient are unclear; multiple

Table 4
Surgery in *GNAO1* patients (literature and personal cases).

Patients	35 (22%) −13 female −12 male
Age at surgery	10 years (average) (4–17 y)
Type of surgery	−32 GPi DBS -1STN DBS −1 STN DBS + GPi DBS + pallidotomy −1 primary pallidotomy
Indication for surgery	−17/35 refractory SD (emergency placement) −12/35 MD exacerbations recurrence/previous SD/ preogressive dystonia −6/35 NA
Outcome	−33/35 clear clinical benefit −1/35 need STN DBS and pallidotomy after GPi DBS (pt 2) −31/35 no recurrence of SD or severe exacerbations during follow up (4 SD recurrence because of complications [7,12,21,34])
Complications/adverse effects:	−5 infections (need for re-implantation in 1 pt) ([7,12,21,34], pt 5) −3 leads or generator dislocation/wires erosion with need for repositioning in 3 pt[7,12,21] −2 bradykinesia [18,35] −1 seizure (patient already known for epilepsy) [22]
Genotype	c.625C > T; p.Arg209Cys [6 pts] c.724-8G > A [6 pts] c.626G > A; p.Arg209His [4 pts] c.709G > A; p.Glu237Lys [3 pts] c.736G > A; p.Glu246Lys [3 pts] c.626G > T; p.Arg209Leu [2 pts] c.737G > A; p.Glu246Gly [1 pt] c.698A > C; p.Gln233Pro [1 pt] c.723+1G > T [1 pt] c.139A > G; p.Ser47Gly [1 pt] c.611G > T; p.Gly204Asp [1 pt] c.620C > T; p.Ser207Phe [1 pt] c.607G > A; p.Gly203Arg [1 pt] c.124 G > A [1 pt] c.617G > A; p.Arg206Gln [1 pt] c.737A > T, p.Glu246Val [1 pt] c.765dupT; p.Asn256* [1 pt]

neuroimaging studies revealed no misplaced leads and stimulation parameters were gradually increased over time. Finally, no hardware complications were detected. However, the patient presented with multiple severe infections, with respiratory and systemic complications due to long hospitalization. The persistence of multidrug-resistant systemic infections is a possible cause of MD and DBS failure worsening.

In our cases, the response to DBS was evaluated by clinical assessment, supported by video recording and quantifying the frequency of paroxysmal episodes and SD after surgery. Overall, patients experienced relief from severe exacerbations with a return to baseline function and, in most cases, mild clinical improvement. In all except one, DBS allowed the reduction of the MD hyperkinetic component, with a relevant and consensual reduction of the number and intensity of MD exacerbations, hospitalizations, and administration of drugs. When considering the entire cohort, no recurrence of severe MD exacerbations was seen in almost all patients after surgery, including those who experienced elective surgery. Good to excellent response to DBS was also seen in most other dystonic patients.

However, total suspension of drug treatment was not attempted in our patients. Subjects treated acutely because of SD (ICU) were gradually weaned from drug therapy (continuous intravenous sedatives, intubation, muscle relaxants); however, the pharmacological treatment for MD has been maintained in the long-term follow-up. Reviewing personal and literature videos, we observed that the reduction, sometimes remarkable, of the dyskinesias is not usually associated with a recovery of the hand's intentional activity. One patient with progressive dystonia [18] experienced mild worsening of dystonia in the absence of device malfunctioning, while SD recurrences after surgery (months to years) appeared in 4 patients [7,12,21,34], all related to hardware malfunction. Reintervention was effective but, unfortunately, 2 patients died after a short period.

When considering complications, 10 presented complications, including infection in 5 patients and lead/wires/generator dislodgement in 3 patients. Moreover, one patient showed one epileptic seizure 3 months after surgery, but the correlation with the implantation is not clear, given that the patient had a history of epilepsy [27]. Two more patients showed bradykinesia and dysarthria, possibly related to DBS programming options [18,35]. Globally, surgery turned out to be an effective intervention with beneficial effects for these patients, although some of the complications and the need for reintervention have been highlighted.

4. Discussion

4.1. *GNAO1* related MD: expanding phenotypes and emerging patterns

We confirmed MD as the core feature in *GNAO1* patients and a clue for diagnosis, characterizing 88.5% (139 patients) of subjects included in this cohort [10,11]. However, since the first description of a patient with a prominent MD in 2016 [9], the spectrum of motor manifestations of *GNAO1* has greatly expanded and our review of the cases and videos brought out some peculiarities of the neurological picture in *GNAO1* patients.

MD typically debuts in infancy and is usually preceded by early-onset hypotonia and developmental delay. Indeed, severe hypotonia and prominent disturbance of postural control seem to be hallmarks of the *GNAO1*-related disease in the early stages, preceding the hyperkinetic MD onset. Moreover, hypokinesia and derangement of postural reactions parallel the emergence of hyperkinetic MD. Impairment of motor achievements suggests an early primary derangement of motor control machinery. Clinical data are often incomplete but, except for a very few cases [20,25,36], patients never achieved independent walking and had only partial/absent trunk and head control. The pattern of presentation and outcome of MD involving both postural control and motor learning is reminiscent of what previously detected in a preclinical model of the *GNAO1* disease, namely the impairment of both Drd2-expressing indirect-pathway neurons (iMSNs) implied in postural background adaptation and Drd1-expressing direct-pathway neurons (dMSNs) implied in motor learning [6].

Moreover, relapsing dyskinetic storms often result in progressive neurological regression and motor skills loss has been reported in nearly 20 cases, suggesting a progressive clinical course, especially in patients with recurrent MD exacerbations. Interestingly, in some of these patients, MRI alterations also showed a progressive trend toward global cerebral atrophy [10,13,37].

A clear characterization of *GNAO1*-related MD is difficult because of a lack of agreement on terminology and incomplete descriptions of MD phenomenology. However, MD is characteristically described as hyperkinetic and includes dystonia, chorea, orofacial dyskinesia, and ballism, often described as fluctuating and susceptible to a wide range of triggers [7,20].

Although dystonia is more widely reported, choreic and dyskinetic features seem to be highly specific for *GNAO1* deficiency. Relapsing, remitting cranial and orofacial dystonia and or dyskinesia with a variable association of dysarthria, dysphagia, buccal and/or tongue dyskinesia, and drooling seem to be a trait of this condition and possibly a focal disorder in less severely affected patients [10].

Other neurological abnormalities, such as ocular movement and parkinsonian features, are now emerging and may be underestimated [7,10,11,21].

The high tendency of this condition to evolve into dystonic-dyskinetic states imposes close surveillance of patients and appropriate counseling with families based on trigger avoidance strategies and recognition of initial SD.

A rarer but emerging GNAO1 phenotype is characterized by milder neurological signs and juvenile or adult-onset dystonia, eventually associated with ataxia, epilepsy, ID and other minor neurological signs. Intronic mutations, which have been associated with these milder phenotypes, may be missed by whole exome sequencing and need appropriate genetic testing to be identified (WGS, sanger sequencing),.

Literature data analysis and detailed phenotyping of a cohort of new patients allowed us to delineate the main emerging patterns in the evolution of MD, showing some variability during MD and timing and severity of exacerbations.

Future prospective studies are needed to confirm the consistency of these clinical patterns and refine the clinical spectrum associated with GNAO1 pathogenic variants.

4.2. Management: current and futures perspectives

Overall, no consensus guidelines are available for treating GNAO1-related MD, which depends on single-center experience. Indeed, several types of MD often combine and change over time in *GNAO1* patients. MD can be chronic, paroxysmal, fluctuating, and may coexist with epilepsy. The concomitant use of antiepileptic drugs may interfere with specific treatments or induce MD as a side effect.

We confirm tetrabenazine as the most widely used and effective pharmacological option, as previously reported [11], especially in improving the basal dyskinetic MD.

New therapeutic strategies are under investigation and new works suggest a potential role of zinc or caffeine [38–40]. However, the MD is often non-responsive to multiple pharmacological interventions and DBS has also been used since 2016 for patients with recurrent MD exacerbations and SD [37]. Though the mechanism of DBS efficacy is only partially understood, GPi-DBS seems to control MDs with a direct anti-dyskinetic effect [41].

Unfortunately, it was not possible to use standardized scales to quantify MD in our patients and evaluate DBS efficacy. However, surgery in *GNAO1* patients seems to be effective on the hyperkinetic choreoathetotic and ballic components, particularly in reducing the most serious exacerbations of MD. An optimal stimulation setting could not be identified among DBS patients.

Because some patients who carry specific mutations, such as the p. Arg209Cys and p.Arg209His seem more prone to MD exacerbations, early surgery could prevent the SD from appearing in a subgroup of *GNAO1* patients. However, following the literature, other variables can influence the response to DBS, including intrinsic characteristics of MD, such as age at onset, duration, movement characteristics (fixed, mobile or phasic), and the location of stimulation and settings [42,43].

5. Conclusions

The phenotypic spectrum associated with *GNAO1* mutations has dramatically expanded since its first description, with a wide range of neurologic manifestations. Among all associated phenotypes, infantile choreo-dystonic MD associated with hypotonia, and developmental disorders is prevalent and should prompt research for *GNAO1* mutations. Severe MD exacerbations with multiple triggers are clinical hallmarks, although a growing number of mild non-paroxysmal "dystonic" phenotypes are now emerging.

DBS could be considered a safe and effective procedure in controlling severe choreic MD exacerbations in these patients. Sustained response to DBS has also been seen in patients with severe dystonia in the absence of fluctuations. It might be reasonable to recommend GPi-DBS when hyperkinetic MD becomes severe or as an elective treatment in a subset of patients harboring specific variants.

5.1. What this paper adds

- Severe hypotonia seems to be a hallmark in the early stages
- Milder non-paroxysmal dystonic phenotypes are now emerging
- Gpi-DBS could be considered an effective procedure in controlling severe MD exacerbations
- MRI shows, especially in severe cases, some recurrent findings

5.2. Limitations and strengths

This study includes an updated review of the literature. In addition, 11 new cases have been described, obtaining a final cohort of 157 *GNAO1* patients. Published and unpublished videos were re-analyzed to characterize MD and clinical course better. Limitations of this study include the lack of standardized scales for MD evaluation in our patients. In fact, as is often the case with pediatric MDs, available rating scales appear to be not adequate to fully evaluate the level of improvement after DBS in the GNAO1 pediatric population (motor and non-motor developmental aspects, better global functioning even without dramatic changes in MD severity, mixed movement disorder).

The BFMDRS, which has been used in 4 of our cases and other literature patients, is not suitable for the complete assessment of hyperkinetic mixed MD in the GNAO1 pediatric population. Therefore, clinical assessment, supported by video recording remains the primary tool for evaluating these conditions. Creating a new tool for assessing pediatric movement disorders, even in the context of neurodevelopmental disorders, is desirable for future research.

Moreover, we point out that our work and conclusion could be limited by relatively brief term follow-up of part of patients, and by heterogeneous use of terms regarding MD phenomenology in literature.

Authors' roles

VL, SG and MN conceived the study protocol and drafted and revised the manuscript. MN, SG, SM interpreted the data and performed the data analysis. MdR, TG, AC, LP, FN, EM, GZ, NN, revised and edited the final version of the manuscript. All authors read and approved the final manuscript.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2023.105405.

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