Parkinsonism and Related Disorders 61 (2019) 19–25

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Review article

Phenomenology and clinical course of movement disorder in *GNAO1* variants: Results from an analytical review

Tommaso Schirinzi[a,b,*,1], Giacomo Garone[a,f,1], Lorena Travaglini[a], Gessica Vasco[a], Serena Galosi[c], Loreto Rios[d], Claudia Castiglioni[d], Claudia Barassi[d], Domenica Battaglia[e], Maria Luigia Gambardella[e], Laura Cantonetti[a], Federica Graziola[a,b], Carlo Efisio Marras[a], Enrico Castelli[a], Enrico Bertini[a], Alessandro Capuano[a,2], Vincenzo Leuzzi[c,2]

[a] Department of Neurosciences, IRCCS Bambino Gesù Children Hospital, Rome, Italy
[b] Department of System Medicine, University of Roma Tor Vergata, Rome, Italy
[c] Department of Pediatrics and Child Neurology and Psychiatry, Sapienza University of Rome, Rome, Italy
[d] Departamento de Neurología Pediátrica, Clínica Las Condes, Santiago, Chile
[e] Department of Child Neurology and Psychiatry, Fondazione Policlinico Universitario Gemelli, Catholic University of Rome, Italy
[f] University Hospital Pediatric Department, Bambino Gesù Children's Hospital, University of Rome Tor Vergata, Rome, Italy

ARTICLE INFO

Keywords:
GNAO1
Status dystonicus
Chorea
Dystonia
Children movement disorders
Movement disorder emergencies

ABSTRACT

GNAO1 variants were recently discovered as causes of epileptic encephalopathies and heterogeneous syndromes presenting with movement disorders (MDs), whose phenomenology and clinical course are yet undefined. We herein focused on *GNAO1*-related MD, providing an analytical review of existing data to outline the main MD phenomenology and management, clinical evolution and genotype-phenotype correlations.

Reviewing 41 previously published patients and assessing 5 novel cases, a comprehensive cohort of 46 patients was analyzed, reassuming knowledge about genotypes, phenotypes, disease course and treatment of this condition. *GNAO1*-related MD consisted of a severe early-onset hyperkinetic syndrome, with prominent chorea, dystonia and orofacial dyskinesia. Symptoms are poorly responsive to medical therapy and fluctuate, with critical and life-threatening exacerbations, such as status dystonicus. The presence of a choreiform MD appears to be predictive of a higher risk of movement disorder emergency. Surgical treatments are sometimes effective, although severe disabilities persist. Differently from the early infantile epileptic encephalopathy phenotype (associated with loss of function variants), no clear correlation between genotype and MD phenotype emerged, although some variants recurred more frequently, mainly affecting exons 6 and 7.

1. Introduction

GNAO1 gene encodes the α subunit of heterotrimeric guanine nucleotide-binding protein (G_i protein), a membrane protein widely expressed in the central nervous system involved in signal transduction. In fact, G_i proteins modulate inhibitory signaling of many neurotransmitters, including GABA, adenosine and dopamine, therefore being crucial for several brain functions [1,2]. Basically, such G_i protein inhibits the adenylyl cyclase, decreasing the production of cyclic adenosine monophosphate (cAMP); however, it may further inhibit the N-type ($Ca_v2.2$) and P/Q type calcium channels, or directly prevent neurotransmitters release at synaptic level [3].

In 2013 Nakamura et al. described four de novo heterozygous missense *GNAO1* variants causative of severe early onset epileptic encephalopathy (EOEE); however following reports revealed a larger and heterogeneous phenotypic spectrum, including mixed syndromes with MDs, development delay, MRI brain abnormalities, inconstant seizures [4]. Of interest, it has recently been demonstrated that epileptic encephalopathy is mostly related to *GNAO1* loss of function (LOF) variants, while gain of function (GOF) heterozygous variants predominantly underline the manifestation of MDs with or without epilepsy [1].

* Corresponding author. Neurology Unit, Department of Systems Medicine, University of Rome Tor Vergata, via Montpellier 1, 00133, Rome, Italy. Unit of Neuromuscular and Neurodegenerative Diseases, Department of Neurosciences, Bambino Gesù Children's Hospital, Piazza Sant'Onofrio, Rome, Italy.
E-mail address: t.schirinzi@yahoo.com (T. Schirinzi).
[1] These authors equally contributed.
[2] These authors are equally senior.

https://doi.org/10.1016/j.parkreldis.2018.11.019
Received 1 August 2018; Received in revised form 5 November 2018; Accepted 9 November 2018

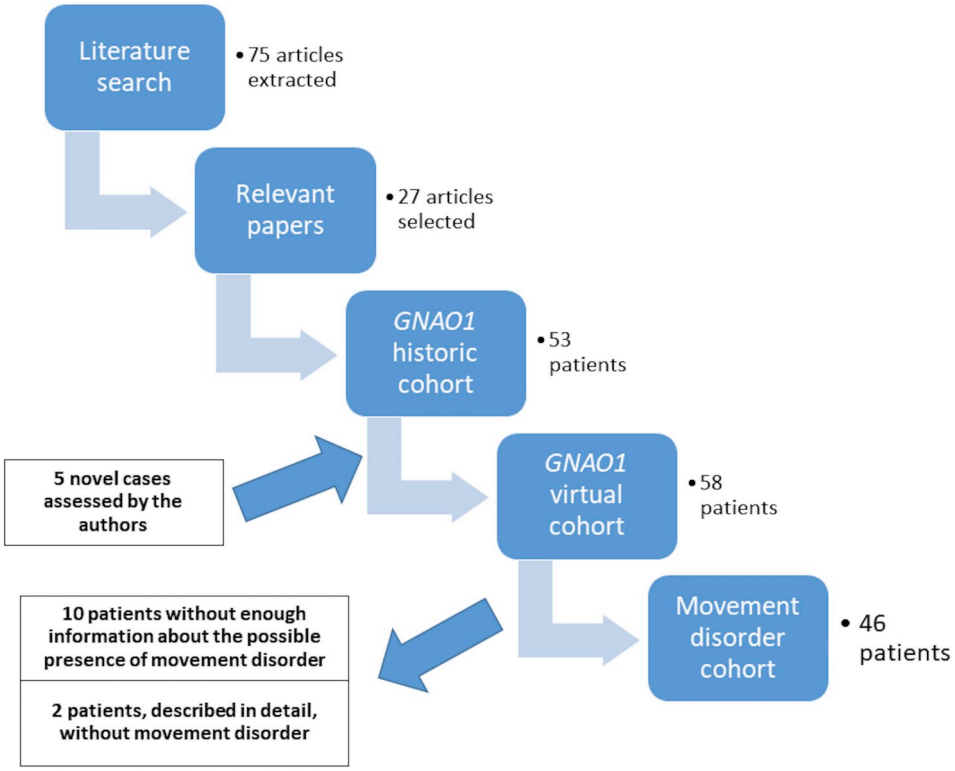

Fig. 1. Inclusion criteria of cases from literature.

Existing literature mainly describes *GNAO1*-related MD as a childhood choreo-dyskinetic syndrome with associated features [4,5], although a more detailed clinical profile has not been yet defined, as well as disease natural history. In fact, many other conditions, such as cerebral palsy, acquired basal ganglia disease, metabolic encephalopathies, mitochondrial diseases or other genetic disorders (e.g. *ADCY5*, *NKX2-1*, *PDE10A* or *STXBP1*-related conditions) [5,6] may have similar presentations, making differential diagnosis challenging. Indeed, *GNAO1* together with *ADCY5*, *PDE10A*, *GPR88*, *GNAL*, constitute a group of genes causing heterogeneous disorders whose pathophysiology probably underlies the disruption of the post-synaptic G_i protein –cAMP pathway in striatal medium spiny neurons [3,6,7].

In this study, we provided a comprehensive analysis on the main genetic and clinical features of all cases of *GNAO1*-related MD so far reported, including 5 unreported patients. In facts, we aimed at delineating phenomenology, clinical course and management of MDs in this condition, evaluating possible genotype-phenotype correlations in the light of recent acquisitions about the functional behavior of several *GNAO1* variants.

2. Methods

To collect all patients with *GNAO1*-related MD, an in-depth literature search using the Medline database was performed. Keywords "*GNAO1*", "*GNAO1*" *plus* "movement disorder", "*GNAO1*" *plus* "chorea", "*GNAO1*" *plus* "epilepsy" and "GNAO1" *plus* "epileptic encephalopathy" were used.

All patients with pathogenic *GNAO1* variants in whom a description of the MD phenotype was available were included. Patients reported without an exhaustive delineation of the MD were excluded. In addition, 5 patients assessed by the authors were included. Genetic analysis was performed for diagnostic purpose by a Custom Enrichment panel for more than 100 genes related to pediatric MD (Case 4, Supplementary File 1 was diagnosed through a panel for epilepsy). For these cases, all procedures accorded local ethical standards and the ethical principles of Helsinki declaration. Involved subjects and their relatives offered the consent for case reporting.

From both previously reported and novel cases, we collected data on the characteristics of the MD (including age of onset, phenomenology classification, clinical course, medical and/or surgical therapies), neuroimaging findings, epileptic features (if present), follow-up information and genetic background. According to Feng et al. [1], which used inhibition of cAMP production as the functional readout to assess the mutant proteins, all reported variants were classified as LOF, partial loss of function (PLOF), normal function (NF), GOF or of unknown function (UF), (see Feng et al., 2017 [1] and 2018 [3] for a comprehensive review of the functional behavior of known *GNAO*1 variants). Additionally, we used SIFT (http://sift.jcvi.org), Polyphen-2 (http://genetics.bwh.harvard.edu/pph2/) and CADD (http://cadd.gs.washington.edu/home) bioinformatics tools to predict the pathogenicity of those variants classified as NF and UF.

A descriptive statistical analysis of data collected was performed. In addition, a logistic regression analysis model to assess the predictive variables associated with a higher risk of the occurrence of MDs emergencies was applied. Candidate clinical variables were tested to identify significant differences between patients with and without MD emergencies. After reviewing for appropriateness, the χ2-and Student's *t* tests were used for categorical and continuous variables, respectively. Inclusion of potentially predictive variables in the logistic model was based on clinical and biological plausibility and significant or nearly significant differences on χ^2 and *t* tests. Variables with extremely unbalanced distribution in the two groups (frequency 0% in one group) were excluded. Adjusted odds ratios (O.R.) and 95% confidence intervals (C.I.95%) were used as measures of effect. The statistical significance was set at $p < 0.05$.

MYSTAT® software (*Systat Software Inc.*, San Jose, California) was used to perform all statistical analyses.

Table 1
Main clinical and demographic features of patients with *GNAO1*-related movement disorder. †Available for 40 out of 46 patients. ‡This proportion considers only the 46 patients with a described movement disorder.

Sex	
Female	27(58.7%)
Male	19(41.3%)
Movement disorders features	
Age in months at MD onset† [mean(median) ± SD]	24.2(17) ± 23.3
Chorea	27(58.7%)
Dystonia	30(65.2%)
Dyskinesia	29(63%)
MD emergencies	21(45.7%)
Need for intensive care hospitalization	19(41.3%)
Surgical treatment	10(21.7%)
Neuroimaging Features	
Cortical atrophy	21(45.7%)
White matter abnormalities	18(39.1%)
Basal ganglia abnormalities	3(6.5%)
Epileptic features	
Epilepsy	22(47.8%)
Epileptic encephalopathy	9(19.6%)‡
Age in months at epilepsy onset [mean(median) ± SD]	28.9(3) ± 43.6
Total seizure control	10(45.4%)
Partial seizure control	1(4.5%)
Intractable seizures	5(22.7%)
No data	6(27.2%)
Follow up data	
Death	4(8.7%)
Age in years at exitus [mean(median) ± SD]	4.8(4) ± 3.8
Age in years at last follow up [mean(median) ± SD]	6.9(5) ± 4.8

3. Results

3.1. GNAO1-related movement disorder cohort

Through the literature search, a total of 77 articles were collected. Among these, 27 articles, appeared between 2013 and 2018 and describing a total of 53 patients, were relevant for our purposes (Supplementary Table S1) [2,4,5,8–31]. Ten patients reported in 7 different papers [8–14] were excluded because little or no information about the possible presence of MD was provided. In addition, we excluded 2 out of the 4 patients described in detail by Nakamura et al. [2] because no MD was reported (Fig. 1).

In addition to previously reported cases, we included 5 novel patients who were assessed in 4 different Institutions (see Supplementary File 1 for a detailed clinical history of the previously unreported patients). As a result, a MD phenotype was found to be described in 46 out of 58 so far reported patients (79%, including the 5 currently described patients). This virtual MD cohort (27 females, male-to-female ratio 0.7) was finally considered (Table 1).

3.2. Movement disorder phenotype and clinical course

The mean age at MD onset (available for 40 patients) was 24 months, but a wide variability was found (range from 3 months to 8 years). Symptomatology mainly consisted of a mixed hyperkinetic syndrome, encompassing different combination of dystonia, choreoathetosis and "dyskinetic movements" in 29 out of 46 cases (63%). In 8 patients, the single presence of choreoathetosis was reported; 5 patients were reported to show only dystonia and in 4 cases the MD phenotype was described as "dyskinetic" or the occurrence of stereotyped dyskinetic movements was reported. In the overall cohort, dystonic features were most frequently reported to be a component of the MD (30 patients, 65.22%), followed by dyskinesias (29 patients, 63.04%) and choreoathetosis (in 27, 58.7%). In 16 patients (34.8%), the presence of oro-facial dyskinesias was reported and in 4 patients (8.7%) myoclonus or unspecified jerky movements were described.

In 21 cases (45.7%), the occurrence of a movement disorders emergency (namely status dystonicus) was reported, requiring intensive care unit (ICU) admission in 19 cases. Both spontaneous or trigger-induced (excitement, stress, intercurrent illness, infections, fever, pain) exacerbations were reported [4,17,21,22].

Mortality was relevant, with 4 patients (8.7%) who deceased at the mean age of 4.72 years (Table 1). Causes of death were respiratory complications [2,17], sepsis [17] or rhabdomyolysis with renal failure [4]. Surviving patients frequently shows severe motor disability [16,17,25], epilepsy [4,5,16,25], mental retardation [2,16,17,20,25], respiratory, speech and feeding problems [16,17], needing significant supportive therapies and cares.

3.3. Movement disorder management

In 10 patients (21.74%) a satisfactory management of the MD was obtained with oral treatment. Overall, tetrabenazine was the most used and effective drug [4,5,17,18,23]. Moreover, variable effects on management of hyperkinesias were reported with phenobarbital, benzodiazepines (clonazepam, diazepam), L-DOPA, neuroleptics (haloperidol, risperidone) and antiepileptics (topiramate, carbamazepine, valproate) [5,17,22,24–26]. 10 patients presenting with severely medical-refractory MD required surgical treatment. 9 of them received the Globus pallidus internus deep brain stimulation (GPi-DBS); the bilateral surgical pallidotomy was instead performed in the remaining one. GPi-DBS has been reported to generally reduce the frequency and severity of MD exacerbations, although in the absence of complete remission [18,21,23,24,27]. Pallidotomy also partially improved MD in that single case **(case 1,** Supplementary File 1**).**

3.4. Neuroimaging data

In 16 cases, normal brain MRI was described. In the remaining cases, a constellation of unspecific findings was reported, namely white matter abnormalities in 18 patients (39.1%, including thin corpus callosum or hypomielination), pallidal hypointensities in 3 cases (6.5%) and cortical atrophy in 21 patients (45.7%).

3.5. Associated epileptic features

Epilepsy was comorbid with movement disorders in 22 out of the 46 patients (47.8%). The onset of seizures preceded the MD manifestation in 8 cases and followed it in 10 patients (this information was missing in 5 patients). The mean age of epilepsy onset (reported in 20 cases) was 28.85 months (range: 1st month of life to 10 years). Nine patients presented with EOEE (early onset epileptic encephalopathy), including 2 cases of early infantile epileptic encephalopathy with burst-suppression (Ohtahara syndrome) and 2 patients with West syndrome (infantile spasms). Seven patients presented focal seizures and 3 patients suffered from generalized tonic-clonic seizures. In the remaining 3 cases, the epileptic phenotype was not specified. In 10 patients, a complete seizure control was obtained, 1 patient reached a partial control on antiepileptic treatment and in 5 patients the epilepsy was described as intractable, no data being available on seizure control in the remaining 6 cases.

3.6. Genetic background

A total of 20 different *GNAO1* variants were accounted among the 46 patients. The array of the different *GNAO1* variants and their functional behavior is summarized in Fig. 2, while Fig. 3 shows the frequency of the different variants encountered. Seven variants have been reported to have a GOF effect, 4 a LOF or PLOF effect and 14 have been reported not to alter protein function, while the functional effect of the remaining 21 is uncertain. 18 patients were found to harbor GOF variants (39.1%), 14 NF variants (30.43%), 3 LOF and 2 PLOF variants, while 9 patients (19.57%) were carriers of UF variants. About 90% of

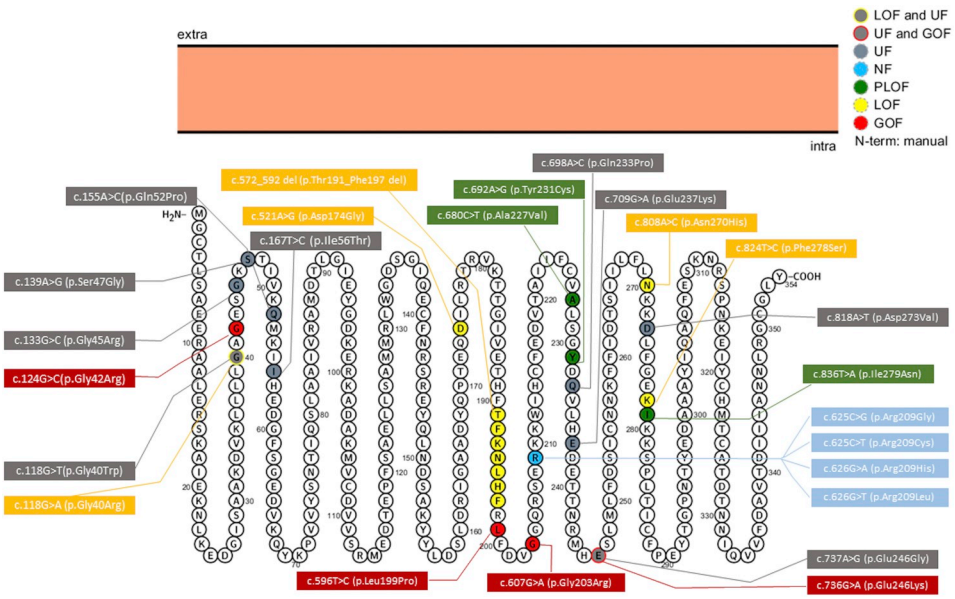

Fig. 2. Membrane topology and distribution of the reported variants in *GNAO1* (modified from Danti et al. [4]). Membrane topology was predicted using the Protter online tool [33] (P09471, GNAO_HUMAN). Functional behavior of the variants is classified according to Feng et al. [1]. GOF: gain of function, LOF: loss of function, PLOF: partial loss of function, NF: normal function, UF: unknown function.

the variants clustered in exons 6 and 7, including those affecting codons 209 and 246, which together account for more than 50% of cases. In addition, we report on a novel missense variant, the c.818 A > T (p.Asp273Val) transversion, which has not been previously described (Case 4, Supplementary File 1). Supplementary Table S2 reassumes the results of in silico pathogenicity prediction tests for all NF and UF variant alleles.

Considering all patients so far reported, with or without MD, it emerged that patients with the NF variants c.626G > T and c.625C > G (p.Arg209Leu) and c.625C > T (p.Arg209Cys) were all reported to be affected by MD ($p = 0.028$), showed a lower frequency of epilepsy compared to patients harboring different variants ($p = 0.009$), and were not reported to develop EOEE. Patients harboring LOF or PLOF showed a higher frequency of epilepsy and EOEE, while the presence of a GOF variant was not associated with a significant difference in the frequency of MD, epilepsy or EOEE (Table 2).

3.7. Logistic regression analysis

Six variables were included in the logistic regression model designed to identify clinical predictors of the occurrence of MD emergencies: sex, presence of chorea, dystonia, dyskinesia, occurrence of epilepsy and the presence of a GOF variant. According to our model (Table 3), the presence of chorea appeared to be significantly associated with a higher risk of MD emergencies, while the other variable did not significantly modify the risk of MD emergencies.

4. Discussion

Since the first description in 2013 [2], the number of patients with *GNAO1*-related neurological conditions has rapidly grown. Initially described as a novel form of EOEE (early infantile epileptic encephalopathy, type 17, MIM 615473) [2,12,15,16], it has become

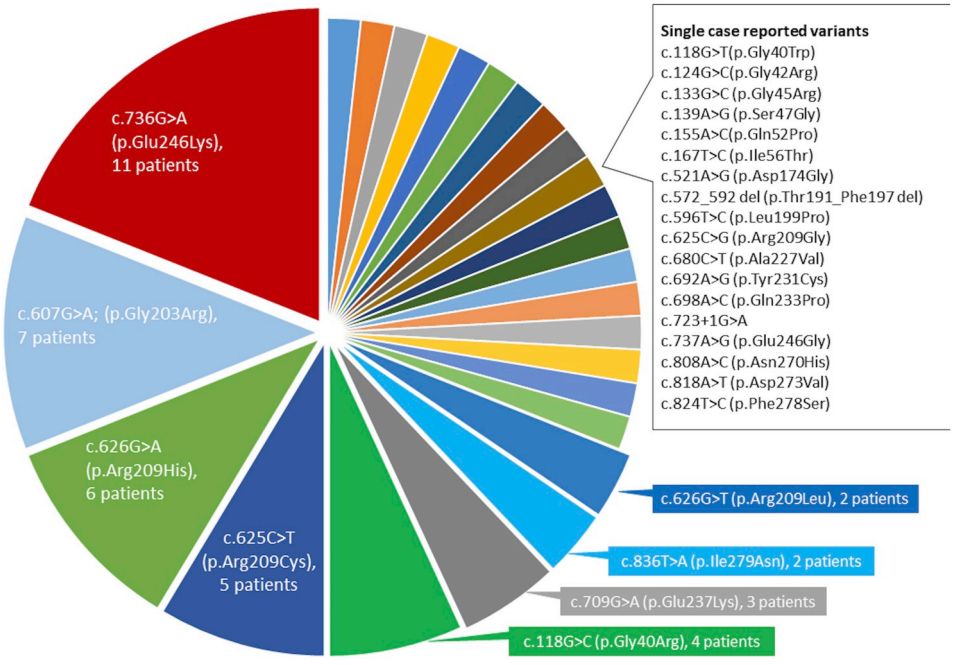

Fig. 3. Frequency distribution of the different *GNAO1* variants described so far.

Table 2
Frequency of movement disorder, epilepsy and early-onset epileptic encephalopathy (EOEE) in patients harboring variants with different functional behavior. All patients carrying *GNAO1* variants so far reported have been included (58 cases). In rows are indicated the three main clinical features considered in the population (movement disorder: observed in 46 patients; epilepsy: observed in 34 patients; EOEE: observed in 18 cases). In columns are expressed the number of cases grouped per genotype (GOF, non-GOF, LOF/PLOF, non-LOF/PLOF, NF, non-NF); the percentage in brackets indicates the frequency of phenotype in that genetic subgroup (example: in the first row, of 34 cases with "epilepsy" phenotype, 10 carried GOF variants; these 10 patients were the 52.63% of the GOF carriers population, including 19 total individuals). P values are based on χ^2-test and reflect the comparison of the relative frequency of movement disorder, epilepsy and EOEE in each group of mutation *versus* the frequency of the same feature amongst all other cases. Statistically significant values are marked in bold characters. GOF: gain of function, LOF: loss of function, PLOF: partial loss of function, NF: normal function.

	GOF (n = 19)	non-GOF (n = 39)	Total (n = 58)	*p*
Epilepsy	10 (52.63%)	24 (61.53%)	34	0.52
Movement disorder	17 (89.47%)	29 (74.36)	46	0.18
EOEE	4 (21.05%)	14 (35.9%)	18	0.25
	LOF or PLOF (n = 10)	non-LOF/PLOF (n = 48)	Total (n = 58)	*p*
Epilepsy	10 (100%)	24 (50%)	34	**0.003**
Movement disorder	6 (60%)	40 (83.33%)	46	0.1
EOEE	8 (80%)	10 (20.83%)	18	< **0.001**
	NF (n = 14)	non-NF (n = 44)	Total (n = 58)	*p*
Epilepsy	4 (28.57%)	30 (68.18%)	34	**0.01**
Movement disorder	14 (100%)	32 (72.72%)	46	**0.03**
EOEE	0(0%)	18 (40.90%)	18	**0.004**

Table 3
Multiple logistic regression model for the risk of movement disorders emergencies in patients with *GNAO1*-related movement disorders. GOF: gain of function.

Independent Variable	p-value	Odds Ratio	Standard Error	95% confidence interval	
				Lower	Upper
GOF variant	0.3	0.3	0.3	0.1	2.1
Sex	0.5	54.7	0.5	0.1	3.7
Chorea	0.001	54.7	67.4	4.9	611.3
Dystonia	0.8	0.8	0.8	0.1	5.8
Dyskinesia	0.3	3.4	3.6	0.4	27.8
Epilepsy	0.5	0.5	0.5	0.1	3.4

rapidly clear that *GNAO1* encephalopathy is associated with a broad spectrum of neurological phenotypes, with various combinations of epilepsy, developmental delay and hyperkinetic MD [5,17–21]. Our review shows that a MD phenotype involves almost 80% of patients. The presence of MD was reported in at least one additional patient [12], but details provided are poor to include him in our analysis. Given its high prevalence, MD appears to be a core feature of *GNAO1* encephalopathy, and it has been observed in the absence of seizures in about 40% of patients so far described. Based on the functional data of 15 *GNAO1* variants, it has been recently postulated that LOF variants are associated with a predominant epileptic phenotype, presenting as EOEE, whereas GOF variants prominently express as a movement disorder [1]. Because of the lack of information about the possible presence of MD in a significant proportion of *GNAO1* patients and absent knowledge about the functional behavior of a quarter of the variants reported, it is difficult to speculate about the real prevalence of MD among patients harboring GOF, LOF or NF *GNAO1* variants. However, considering all the patients so far reported, variants affecting the arginine 209 residue seem to be significantly associated with a prominent MD phenotype, with low prevalence of epilepsy and no occurrence of EOEE. Other mutation hotspots prominently causing MD are Glycine 203 and Glutamate 246 residues [3]. By contrast, it is evident that epilepsy, especially the EOEE presentation, is significantly more frequent in patients with LOF or PLOF variants. GNAO1 protein is normally responsible for the reduction of cAMP levels, via the inhibition of adenylyl cyclase; therefore such LOF or PLOF variants, leading to an enhancement of cAMP-mediated signaling, may explain the pathogenesis of *GNAO1*-related EOEE. Conversely, it is rather unclear how NF variants can cause the MD. Probably, we should consider that the inhibition of the cAMP pathway, commonly used as a functional readout for the protein, is not sufficient to assess its real biological activity. Indeed, GNAO1 protein also controls N-type and P/Q-type calcium channels and synaptic vesicle release, which may be likewise critically involved in the pathophysiology of MD [1,3].

The course of MD has been described as severe and fluctuating, characterized by spontaneous or trigger-induced exacerbations [4,17,21,22], frequently requiring ICU admission and sedation [4,20,23]. According to our model, the occurrence of MD emergencies is favored by the presence of a choreoathetosic phenotype, and is less frequent in patients with other forms of hyperkinetic MD. In this regard, it is noteworthy that MD terminology and classification is a critical issue in childhood-onset MD literature [32], because of the lack of consensus on the correct utilization of derived terms. Consequently, the heterogeneous classification of MD phenomenology in different reports could limit the validity of our conclusions.

By contrast, no genetic factor has been found to modify the risk of MD emergencies. As mentioned above, the poor genotype-phenotype correlation probably reflects the still partial comprehension of the functional behavior of a consistent proportion of the pathogenic variants and the heterogeneity in patients' phenotyping. However, it is evident that MD exacerbations are a severe and frequent complication of this condition, further worsened by poor responsiveness to medical treatments. Tetrabenazine resulted the most used and effective drug [4,5,17,18,23], probably due to its wide-spread effect in reducing G_i signaling through the depletion of biogenic amines [3]. Again, other medications commonly used for management of MD provided very modest efficacy. In patients with severely refractory MD, GPi-DBS has been reported to generally reduce the frequency and severity of MD exacerbations, although in the absence of complete remission [18,21,23,24,27]. Unfortunately, available data did not allow claiming the efficacy of such intervention in preventing status dystonicus, MD emergencies and further neurological deterioration, being indeed necessary specific prospective controlled studies. However, DBS and, to a lesser extent, the surgical pallidotomy could represent promising therapeutic options for patients with *GNAO1*-related MD at early phases. At this regard, the severity of the condition should be carefully considered, in face of the high mortality and disability of surviving patients.

5. Conclusions

GNAO1 variants are causative of a severe early-onset hyperkinetic disorder. Dystonia, dyskinesias and choreoathetosis were most frequently reported, followed by oro-facial dyskinesias and myoclonus. Movement disorders often precipitate, causing life-threatening emergencies (including status dystonicus). Response to medical therapy is incomplete, while bilateral GPi-DBS or pallidotomy provide partial efficacy, although long-term data are still lacking. Despite the consistent emerging correlations between the EOEE phenotype and the loss of the inhibitory function of GNAO1 protein, the correlation between the genotype and the MD phenotype are yet poorly understood, as well as

the functional mechanisms underlying MD development. *GNAO1* defects should be considered in the differential diagnosis of conditions presenting with developmental delay, neurological deterioration and severe hyperkinetic disorder during the first years of life. In particular, exons 6 and 7 are mutational hotspots to be preliminary evaluated in that cases.

Declarations of interest

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Final disclosures

All authors have approved the final article. They also declare no conflicts of interest. No funding has been received for this study.

Acknowledgements

Authors wish to thank all the Neurogenetic Lab team of the Pediatric Neurology Unit and Laboratories, A. Meyer Children's Hospital – University of Florence, directed by professor Renzo Guerrini, for having performed the mutational analysis in patient 1 of our series.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2018.11.019.

References

[1] H. Feng, B. Sjogren, B. Karaj, V. Shaw, A. Gezer, R.R. Neubig, Movement disorder in GNAO1 encephalopathy associated with gain-of-function mutations, Neurology 89 (2017) 762–770, https://doi.org/10.1212/WNL.0000000000004262.

[2] K. Nakamura, H. Kodera, T. Akita, M. Shiina, M. Kato, H. Hoshino, H. Terashima, H. Osaka, S. Nakamura, J. Tohyama, T. Kumada, T. Furukawa, S. Iwata, T. Shiihara, M. Kubota, S. Miyatake, E. Koshimizu, K. Nishiyama, M. Nakashima, Y. Tsurusaki, N. Miyake, K. Hayasaka, K. Ogata, A. Fukuda, N. Matsumoto, H. Saitsu, De Novo mutations in GNAO1, encoding a Galphao subunit of heterotrimeric G proteins, cause epileptic encephalopathy, Am. J. Hum. Genet. 93 (2013) 496–505, https://doi.org/10.1016/j.ajhg.2013.07.014.

[3] H. Feng, S. Khalil, R.R. Neubig, C. Sidiropoulos, A mechanistic review on GNAO1-associated movement disorder, Neurobiol. Dis. 116 (2018) 131–141, https://doi.org/10.1016/j.nbd.2018.05.005.

[4] F.R. Danti, S. Galosi, M. Romani, M. Montomoli, K.J. Carss, F.L. Raymond, E. Parrini, C. Bianchini, T. McShane, R.C. Dale, S.S. Mohammad, U. Shah, N. Mahant, J. Ng, A. McTague, R. Samanta, G. Vadlamani, E.M. Valente, V. Leuzzi, M.A. Kurian, R. Guerrini, GNAO1 encephalopathy: broadening the phenotype and evaluating treatment and outcome, Neurol. Genet. 3 (2017) e143, https://doi.org/10.1212/NXG.0000000000000143.

[5] R. Arya, C. Spaeth, D.L. Gilbert, J.L. Leach, K.D. Holland, GNAO1-associated epileptic encephalopathy and movement disorders: c.607G > A variant represents a probable mutation hotspot with a distinct phenotype, Epileptic Disord. 19 (2017) 67–75, https://doi.org/10.1684/epd.2017.0888.

[6] M. Carecchio, N.E. Mencacci, Emerging monogenic complex hyperkinetic disorders, Curr. Neurol. Neurosci. Rep. 17 (2017) 97, https://doi.org/10.1007/s11910-017-0806-2.

[7] L. Abela, M.A. Kurian, Postsynaptic movement disorders: clinical phenotypes, genotypes, and disease mechanisms, J. Inherit. Metab. Dis. (2018), https://doi.org/10.1007/s10545-018-0205-0.

[8] T.U.J. Bruun, C.-L. DesRoches, D. Wilson, V. Chau, T. Nakagawa, M. Yamasaki, S. Hasegawa, T. Fukao, C. Marshall, S. Mercimek-Andrews, Prospective cohort study for identification of underlying genetic causes in neonatal encephalopathy using whole-exome sequencing, Genet. Med. 20 (2018) 486–494, https://doi.org/10.1038/gim.2017.129.

[9] Novo De, Mutations in SLC1A2 and CACNA1A are important causes of epileptic encephalopathies, Am. J. Hum. Genet. 99 (2016) 287–298, https://doi.org/10.1016/j.ajhg.2016.06.003.

[10] De novo mutations in synaptic transmission genes including DNM1 cause epileptic encephalopathies, Am. J. Hum. Genet. 100 (2017) 179, https://doi.org/10.1016/j.ajhg.2016.12.012.

[11] P. Gawlinski, R. Posmyk, T. Gambin, D. Sielicka, M. Chorazy, B. Nowakowska, S.N. Jhangiani, D.M. Muzny, M. Bekiesinska-Figatowska, J. Bal, E. Boerwinkle, R.A. Gibbs, J.R. Lupski, W. Wiszniewski, PEHO syndrome may represent phenotypic expansion at the severe end of the early-onset encephalopathies, Pediatr. Neurol. 60 (2016) 83–87, https://doi.org/10.1016/j.pediatrneurol.2016.03.011.

[12] X. Zhu, S. Petrovski, P. Xie, E.K. Ruzzo, Y.-F. Lu, K.M. McSweeney, B. Ben-Zeev, A. Nissenkorn, Y. Anikster, D. Oz-Levi, R.S. Dhindsa, Y. Hitomi, K. Schoch, R.C. Spillmann, G. Heimer, D. Marek-Yagel, M. Tzadok, Y. Han, G. Worley, J. Goldstein, Y.-H. Jiang, D. Lancet, E. Pras, V. Shashi, D. McHale, A.C. Need, D.B. Goldstein, Whole-exome sequencing in undiagnosed genetic diseases: interpreting 119 trios, Genet. Med. Off. J. Am. Coll. Med. Genet. 17 (2015) 774–781, https://doi.org/10.1038/gim.2014.191.

[13] K.L. Helbig, K.D. Farwell Hagman, D.N. Shinde, C. Mroske, Z. Powis, S. Li, S. Tang, I. Helbig, Diagnostic exome sequencing provides a molecular diagnosis for a significant proportion of patients with epilepsy, Genet. Med. Off. J. Am. Coll. Med. Genet. 18 (2016) 898–905, https://doi.org/10.1038/gim.2015.186.

[14] J.H. Rim, S.H. Kim, I.S. Hwang, S.S. Kwon, J. Kim, H.W. Kim, M.J. Cho, A. Ko, S.E. Youn, J. Kim, Y.M. Lee, H.J. Chung, J.S. Lee, H.D. Kim, J.R. Choi, S.-T. Lee, H.-C. Kang, Efficient strategy for the molecular diagnosis of intractable early-onset epilepsy using targeted gene sequencing, BMC Med. Genom. 11 (2018) 6, https://doi.org/10.1186/s12920-018-0320-7.

[15] C.-Y. Law, S.T.-L. Chang, S.Y. Cho, E.K.-C. Yau, G.S.-F. Ng, N.-C. Fong, C.-W. Lam, Clinical whole-exome sequencing reveals a novel missense pathogenic variant of GNAO1 in a patient with infantile-onset epilepsy, Clin. Chim. Acta 451 (2015) 292–296, https://doi.org/10.1016/j.cca.2015.10.011.

[16] I. Talvik, R.S. Moller, M. Vaher, U. Vaher, L.H. Larsen, H.A. Dahl, P. Ilves, T. Talvik, Clinical phenotype of de novo GNAO1 mutation: case report and review of literature, Child Neurol. Open. 2 (2015), https://doi.org/10.1177/2329048X15583717 2329048X15583717.

[17] A.L. Ananth, A. Robichaux-Viehoever, Y.M. Kim, A. Hanson-Kahn, R. Cox, G.M. Enns, J. Strober, M. Willing, B.L. Schlaggar, Y.W. Wu, J.A. Bernstein, Clinical course of six children with GNAO1 mutations causing a severe and distinctive movement disorder, Pediatr. Neurol. 59 (2016) 81–84, https://doi.org/10.1016/j.pediatrneurol.2016.02.018.

[18] N. Kulkarni, S. Tang, R. Bhardwaj, S. Bernes, T.A. Grebe, Progressive movement disorder in brothers carrying a GNAO1 mutation responsive to deep brain stimulation, J. Child Neurol. 31 (2016) 211–214, https://doi.org/10.1177/0883073815587945.

[19] L.A. Menke, M. Engelen, M. Alders, V.J.J. Odekerken, F. Baas, J.M. Cobben, Recurrent GNAO1 mutations associated with developmental delay and a movement disorder, J. Child Neurol. 31 (2016) 1598–1601, https://doi.org/10.1177/0883073816666474.

[20] H. Saitsu, R. Fukai, B. Ben-Zeev, Y. Sakai, M. Mimaki, N. Okamoto, Y. Suzuki, Y. Monden, H. Saito, B. Tziperman, M. Torio, S. Akamine, N. Takahashi, H. Osaka, T. Yamagata, K. Nakamura, Y. Tsurusaki, M. Nakashima, N. Miyake, M. Shiina, K. Ogata, N. Matsumoto, Phenotypic spectrum of GNAO1 variants: epileptic encephalopathy to involuntary movements with severe developmental delay, Eur. J. Hum. Genet. 24 (2016) 129–134, https://doi.org/10.1038/ejhg.2015.92.

[21] S. Yilmaz, T. Turhan, S. Ceylaner, S. Gökben, H. Tekgul, G. Serdaroglu, Excellent response to deep brain stimulation in a young girl with GNAO1-related progressive choreoathetosis, Child's Nerv. Syst. 32 (2016) 1567–1568, https://doi.org/10.1007/s00381-016-3139-6.

[22] S. Sakamoto, Y. Monden, R. Fukai, N. Miyake, H. Saito, A. Miyauchi, A. Matsumoto, M. Nagashima, H. Osaka, N. Matsumoto, T. Yamagata, A case of severe movement disorder with GNAO1 mutation responsive to topiramate, Brain Dev. 39 (2017) 439–443, https://doi.org/10.1016/j.braindev.2016.11.009.

[23] M. Waak, S.S. Mohammad, D. Coman, K. Sinclair, L. Copeland, P. Silburn, T. Coyne, J. McGill, M. O'Regan, R. Selway, J. Symonds, P. Grattan-Smith, J.-P. Lin, R.C. Dale, S. Malone, GNAO1-related movement disorder with life-threatening exacerbations: movement phenomenology and response to DBS, J. Neurol. Neurosurg. Psychiatry 89 (2018) 221–222, https://doi.org/10.1136/jnnp-2017-315653.

[24] C. Marecos, S. Duarte, I. Alonso, E. Calado, A. Moreira, [GNAO1: a new gene to consider on early-onset childhood dystonia], Rev. Neurol. 66 (2018) 321–322.

[25] A. Marce-Grau, J. Dalton, J. Lopez-Pison, M.C. Garcia-Jimenez, L. Monge-Galindo, E. Cuenca-Leon, J. Giraldo, A. Macaya, GNAO1 encephalopathy: further delineation of a severe neurodevelopmental syndrome affecting females, Orphanet J. Rare Dis. 11 (2016) 38, https://doi.org/10.1186/s13023-016-0416-0.

[26] D.C. Schorling, T. Dietel, C. Evers, K. Hinderhofer, R. Korinthenberg, D. Ezzo, C.G. Bonnemann, J. Kirschner, Expanding phenotype of de novo mutations in GNAO1: four new cases and review of literature, Neuropediatrics 48 (2017) 371–377, https://doi.org/10.1055/s-0037-1603977.

[27] C.M. Honey, A.K. Malhotra, M. Tarailo-Graovac, C.D.M. van Karnebeek, G. Horvath, A. Sulistyanto, GNAO1 mutation-induced pediatric dystonic storm rescue with pallidal deep brain stimulation, J. Child Neurol. 33 (2018) 413–416, https://doi.org/10.1177/0883073818756134.

[28] L. Blumkin, T. Lerman-Sagie, A. Westenberger, H. Ben-Pazi, A. Zerem, K. Yosovich, D. Lev, Multiple causes of pediatric early onset chorea-clinical and genetic approach, Neuropediatrics (2018), https://doi.org/10.1055/s-0038-1645884.

[29] R. Dhamija, J.W. Mink, B.B. Shah, H.P. Goodkin, GNAO1-Associated movement disorder, Mov. Disord. Clin. Pract. 3 (n.d.) 615–617. doi:10.1002/mdc3.12344.

[30] A. Okumura, K. Maruyama, M. Shibata, H. Kurahashi, A. Ishii, S. Numoto, S. Hirose, T. Kawai, M. Iso, S. Kataoka, Y. Okuno, H. Muramatsu, S. Kojima, A patient with a GNAO1 mutation with decreased spontaneous movements, hypotonia, and dystonic features, Brain Dev. (2018), https://doi.org/10.1016/j.braindev.2018.06.005.

[31] Y. Takezawa, A. Kikuchi, K. Haginoya, T. Niihori, Y. Numata-Uematsu, T. Inui, S. Yamamura-Suzuki, T. Miyabayashi, M. Anzai, S. Suzuki-Muromoto, Y. Okubo,

W. Endo, N. Togashi, Y. Kobayashi, A. Onuma, R. Funayama, M. Shirota, K. Nakayama, Y. Aoki, S. Kure, Genomic analysis identifies masqueraders of full-term cerebral palsy, Ann. Clin. Transl. Neurol. 5 (2018) 538–551, https://doi.org/10.1002/acn3.551.

[32] A. Arzimanoglou, Movement disorders in children: the need to observe, describe in detail and integrate your findings to the global clinical picture, Eur. J. Paediatr. Neurol. EJPN Off. J. Eur. Paediatr. Neurol. Soc. 22 (2018) 217–218, https://doi.org/10.1016/j.ejpn.2018.01.019.

[33] U. Omasits, C.H. Ahrens, S. Müller, B. Wollscheid, Protter: interactive protein feature visualization and integration with experimental proteomic data, Bioinformatics 30 (2014) 884–886, https://doi.org/10.1093/bioinformatics/btt607.