Epilepsy & Behavior 125 (2021) 108365

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Brief Communication

Epilepsy and related challenges in children with *COL4A1* and *COL4A2* mutations: A Gould syndrome patient registry

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ARTICLE INFO

Article history:
Received 20 September 2021
Accepted 25 September 2021

Keywords:
Gould syndrome
Epilepsy
Stroke
COL4a1
COL4a2
Genetic

ABSTRACT

Recently, patient advocacy groups started using the name Gould syndrome to describe clinical features of *COL4A1* and *COL4A2* mutations. Gould syndrome is increasingly identified in genetic screening panels, and because it is a rare disease, there is a disproportionate burden on families to understand the disease and chart the course for clinical care. Among the chief concerns for caregivers of children with Gould syndrome are the challenges faced because of epilepsy, including severe manifestations such as infantile spasms. To document the concerns of the patient population, the Gould Syndrome Foundation established the Gould Syndrome Global Registry (GSGR).

Methods: The Gould Syndrome Foundation developed questions for the GSGR with iterative input from patients and caregivers. An institutional review board issued an exemption determination before data collection began. Participants were recruited through social media and clinician referrals. All participants consented electronically, and the data were collected and managed using REDCap electronic data capture tools. De-identified data representing responses received between October 2019 and February 2021 were exported and analyzed with IBM SPSS 27 using descriptive statistics (mean, standard deviation, frequency, range, and percent).

Results: Seventy families from twelve countries provided data for the registry, representing 100 affected people (40 adults and 60 children). This analysis represents a subanalysis of the 35 out of 60 children <=18 years of age who reported a history of seizures. Nearly half of these participants were diagnosed with infantile spasms. Participants with epilepsy frequently reported developmental delays (88.6%), stroke (60.0%), cerebral palsy (65.7%), and constipation (57.1%). Ten (28.6%) children use a feeding tube. Despite the fact that more than half of respondents reported stroke, only 34.3% reported ever receiving education on stroke recognition.

Conclusion: Here we describe the development and deployment of the first global registry for individuals and family members with Gould syndrome, caused by mutations in *COL4A1* and *COL4A2*. It is important for pediatric neurologists to have access to resources to provide families upon diagnosis. Specifically, all families with Gould Syndrome must have access to infantile spasms awareness and stroke education materials. The Gould Syndrome Foundation is planning several improvements to this patient registry which will encourage collaboration and innovation for the benefit of people living with Gould syndrome.

1. Introduction

Recently, patient advocacy groups started using the name Gould syndrome to describe clinical features of *COL4A1* and *COL4A2* mutations [1]. Congenital and acquired developmental cerebrovascular defects, including porencephaly and perinatal intracerebral hemorrhages, are frequently observed in individuals with *COL4A1* and *COL4A2* mutations. Additional cerebral manifestations include cortical malformations (schizencephaly and lamination defects) and childhood-onset epilepsy, often complicated by antiepileptic drug resistance and status epilepticus [2,3]. Individuals with Gould syndrome also often present with variable ocular dysgenesis (microphthalmia, microcornea, congenital cataracts, congenital

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https://doi.org/10.1016/j.yebeh.2021.108365
1525-5050/

glaucoma, and optic nerve hypoplasia) [4–6], myopathy (muscle cramps, elevated serum creatine kinase, focal dystrophic lesions), and nephropathy (hematuria, proteinuria, polycystic kidneys, and end-stage renal failure) [7–10]. Thus, Gould syndrome is a severe multisystem connective tissue disorder with broad and variable organ involvement for which there is currently no treatment [11].

Gould syndrome is increasingly identified in genetic screening panels, and because it is a rare disease, there is a disproportionate burden on families to understand the disease and chart the course for clinical care. The Gould Syndrome Foundation began as a Facebook group in June 2018 as a forum where individuals with *COL4A1* or *COL4A2* mutations, or their family members, discussed the challenges and concerns related to this poorly understood condition. In July 2018, the Gould Syndrome Foundation was formed as a 501(c) nonprofit to serve the critical need of providing support to and education to newly diagnosed patients and their families. The Gould Syndrome Foundation established the Gould Syndrome Global Registry (GSGR) to collect comprehensive data from people diagnosed with *COL4A1* or *COL4A2* mutations to facilitate support, education, and research. Notably, among the chief concerns for caregivers of children with Gould syndrome are the challenges faced because of epilepsy, including infantile spasms. To begin to address this concern, we used the GSGR to systematically analyze the prevalence of pediatric seizures and related neurologic disorders among our registry participants.

2. Methods

The Gould Syndrome Foundation developed questions for the GSGR with input from patients and caregivers. Western Institutional Review Board (now WCG IRB) reviewed the protocol before data collection began and issued an exemption determination. Participants were recruited through social media and physician referrals. All participants consented electronically, and the data were collected and managed using REDCap electronic data capture tools [12]. De-identified data representing responses received between October 2019 and February 2021 were exported and analyzed with IBM SPSS 27 using descriptive statistics (mean, standard deviation, range, frequency, and percent).

3. Results

3.1. General characteristics

Seventy families from twelve countries (United States, United Kingdom, Canada, Australia, Austria, Belgium, Denmark, France, Germany, Israel, Netherlands, and South Africa) enrolled in the registry. Respondents were distinguished as: an affected child only ($n = 30$; 2 of which were reported as having passed away), an affected adult respondent only ($n = 16$), an affected parent with one affected child ($n = 19$), an affected parent with two affected children ($n = 4$), and an affected parent with three affected children ($n = 1$). This represented 100 affected people with the defined genetic mutations: adults ($n = 40$) and children ($n = 60$). At the time of survey completion, 10 affected children were adult children who were over 18 years old and 50 affected children were under 18 years old.

3.2. Seizure-related reports in children

Out of the 60 affected children, 35 (58.3%) were under 18 years of age at the time of survey completion and had a history of seizures (i.e., reported seizures, epilepsy, Lennox–Gastaut syndrome, infantile spasms, or electrical status epilepticus in sleep) and were therefore included in the pediatric epilepsy subgroup. Detailed participant characteristics for this subgroup is documented in Table 1. This subgroup is the focus of the analysis that follows.

When examining current seizure types, respondents reported generalized tonic-clonic seizures (57.1%), focal or partial seizures (60.0%), absence seizures (48.6%), myoclonic seizures (42.9%), epileptic spasms (34.3%), and atonic seizures (20.0%). Epilepsy-related testing was frequently reported for affected children, and 97.1% reported undergoing an electroencephalogram (EEG). Most pediatric participants underwent neuroradiological examinations, including brain magnetic resonance imaging (MRI) (97.1%), and many underwent advanced imaging for further characterization of epilepsy with positron emission tomography (PET) (22.9%) and magnetoencephalography (MEG) (14.3%). Overall, 25.7% of participants experienced at least one epilepsy surgery. Out of the participants who indicated they had epilepsy surgery, the type of surgery was indicated as hemispherectomy (33.3%), lesionectomy (22.2%), or vagus nerve stimulation (VNS) surgery (11.1%). Two people also listed "shunt placement" as "other" type of epilepsy surgery.

The most frequently reported specific conditions were developmental delays (88.6%), stroke (60.0%), cerebral palsy (65.7%), and constipation (57.1%). Ten (28.6%) children were reported to require a feeding tube. Despite the fact that more than half of respondents reported stroke, only 34.3% reported receiving education on how to manage stroke. The prevalence of additional relevant conditions is shown in Table 2.

For their treatment teams, the affected children frequently reported having a general neurologist (80.0%) and/or an epileptologist (65.7%). Other members of their treatment team included: physical therapist (85.7%), ophthalmologist (85.7%), general pediatrician (88.6%), occupational therapist (82.9%), speech pathologist (74.3%), gastroenterologist (48.6%), pediatric dentist (37.1%), nephrologist (34.3%), cardiologist (28.6%), developmental pediatrician (25.7%), behavioral therapist (22.9%), specialist dentist (14.3%), pulmonologist (8.6%), and psychiatrist (5.7%).

The school distribution for the children was: 25.7% public school, 11.4% private special education school, 5.7% home school, 2.9% private non-special education school, and 54.2% other, too young for school, or did not respond. The respondents reported 40.0% had an Individualized Educational Plan (IEP), 5.7% had an Individual Family Service Plan (IFSP), 5.7% reported a 504 plan, and 5.7% reported a school behavioral aide. In addition, 20.0% reported a personal care assistant.

When asked what additional resources are on their "wish list" to support their journey with Gould syndrome, 31 out of 35

Table 1
Participant characteristics, pediatric epilepsy subset ($n = 35$).

Age in years, *M* (*SD, range*)	4.6 (3.3, 3–13)
Gender	
Female	14 (40.0%)
Male	21 (60.0%)
Race/	
Non-Hispanic White	29 (93.5%)
Multiple Races	3 (8.6%)
Hispanic White	2 (5.7%)
Asian	1 (2.9%)
Mutation	
COL4A1	30 (85.7%)
COL4A2	5 (14.3%)
Inheritance	
De Novo	19 (55.9%)
Inherited	10 (29.4%)
Unsure/Unknown	6 (14.7%)
Infantile Spasms diagnosis	16 (45.7%)
Electrical status epilepticus in sleep (ESES) diagnosis	9 (25.7%)
Lennox–Gastaut syndrome diagnosis	4 (11.4%)
Epilepsy surgery	9 (25.7%)

All values are shown as *n* (%) unless otherwise noted.

Table 2
Prevalence of conditions in the pediatric epilepsy subset (n = 35).

	n (%)
Developmental delays	31 (88.6%)
Cerebral palsy	23 (65.7%)
Stroke	21 (60.0%)
Constipation	20 (57.1%)
Cortical vision impairment	16 (45.7%)
Microcephaly	16 (45.7%)
Learning disabilities	14 (40.0%)
Cataracts	14 (40.0%)
Intracerebral hemorrhage	13 (37.1%)
Feeding disorder	10 (28.6%)
Clonus	10 (28.6%)
Dystonia	10 (28.6%)
Porencephaly	9 (25.7%)
Gastroesophageal reflux disease	8 (22.9%)
Exotropia	8 (22.9%)
Sleep apnea	6 (17.1%)
Periventricular leukomalacia	6 (17.1%)
Leukoencephalopathy	4 (11.4%)
Microphthalmia	4 (11.4%)
Hydrocephalus	4 (11.4%)
Hematuria	4 (11.4%)

Diagnoses endorsed by at least 4 participants (11.4%) are shown.

Table 3
Respondent wish list.

Theme(s)	Sample Quotations
Accessing academic/ therapeutic services	"I wish my child get physical, speech and Occupational therapy every day. But my insurance allows or pays for only one. I don't know he will improve or not. I will be crying in my mind all the time when he is struggling." – Participant 0001
Accessing academic/ therapeutic services	"wish qualifying for an IEP were easier based on diagnosis wish we had more educated doctors involved" – Participant 0002
Research	"We have been learning more about gene therapies. All clinical trials and therapies we would love to be involved with. We currently have first steps in addition to our awesome doctors." — Participant 0003
Educational resources	"child - information, anxiety and stressed behaviour management, glaucoma management.
Caregiver support	parents - stress management and counselling" – Participant 0004
Caregiver support	"I wish I had a babysitter because I don't have enough time for myself" –Participant 0005
Access to knowledgeable physicians	"Access to specialists in the US who are knowledgeable and can work with our drs in diagnosing [child's] complicated health. Dr Gould is the only one who responds to our physicians and ourselves." —Participant 0006

respondents representing children with epilepsy shared information (Table 3). Most responses fell under the general themes of accessing academic/therapy services, educational resources, caregiver support, research, and access to knowledgeable physicians. Nearly all (94.3%) registry respondents agreed to be contacted for future research projects.

4. Discussion

Here, we describe the development and deployment of the first global registry for individuals and family members with Gould syndrome caused by mutations in *COL4A1* and *COL4A2*. We highlight a pediatric subset of registry participants with a history of seizures and note that 46% of these individuals have been diagnosed with infantile spasms. We describe comorbidities faced in this patient population, their experiences in school and with the medical community, and barriers to accessing clinical, educational, and community service by people with Gould syndrome and their families.

The main limitation of this patient registry is the fact that it is entirely self-reported with no verification of responses against clinical documentation. It is also cross-sectional and limited to participants who speak English. Therefore, not all regions of the world are represented in this sample. People who are already participating in social media support groups where much of the recruiting for the GSGR might be more motivated than those who do not participate in social media groups, which could result in selection bias. In the interest of limiting participant burden, we did not ask for details such as dates of individual symptom onset or comprehensive medication history that would have added depth to this analysis.

The Gould Syndrome Foundation is in the process of advancing the registry by incorporating recommendations of the NIH ClinGen group [13] using Human Phenotype Ontology and other common data elements and validated instruments. The next generation of the GSGR (GSGR 2.0) will be hosted on the Across Healthcare Matrix platform (acrossmatrix.com) and will include electronic health record linkages and genetic report curation. GSGR 2.0 will also have the ability to create sub-studies with other researchers. Despite its limitations, the GSGR provides an important first look into the lives of people with Gould syndrome.

As a patient advocacy group, the primary focus of the Gould Syndrome Foundation is to support awareness of Gould syndrome among clinicians, patients, and the public. This study demonstrates the importance of providing pediatric neurologists with resources to share with families upon diagnosis. Specifically, all families with Gould syndrome must have access to infantile spasms and stroke awareness materials. The Gould Syndrome Foundation website offers extensive evidence-based information, as well as a connection to social media groups for peer-to-peer family support. In addition to the Gould Syndrome Foundation official support services, 16 of our registry respondents reported having a website or social media account related to an affected individual's journey which can be accessed through the Foundation's social media connections. Please visit https://gouldsyndromefoundation.org for more information.

Declaration of Competing Interests

Danielle Boyce serves as a paid consultant for Greenwich Biosciences and Neurocrine. Sheena McGee, Lisa Shank, Sheel Pathak, and Douglas Gould have no conflicts of interest to declare.

Acknowledgements

The authors would like to thank all of the registry participants for making this research possible, and Cathy McMahen for her formatting and editing expertise.

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