EXPRESSION OF SERUM ANTI-GANGLIOSIDE ANTIBODY IN PATIENTS WITH GUILLAIN-BARRÉ SYNDROME AND ITS RELATIONSHIP WITH CLINICAL FEATURES

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ABSTRACT

Introduction: *In this study, we investigated the expression of serum anti-ganglioside antibodies in patients with Guillain-Barré syndrome (GBS) and its relationship to clinical features.*

Methods: *A total of 104 patients with GBS were retrospectively studied and 49 patients who underwent anti-ganglioside antibody testing were analysed.*

Results: *Serum anti-ganglioside antibodies were detected in 67.3% of GBS patients. The average age of onset was 48.8+16.1 years for anti-ganglioside antibody positivity, and 35+16.1 years for antibody negativity (P<0.05). The expression ratio of anti-GM1 antibodies in acute inflammatory demyelinating polyneuropathy (AIDP) was 42.0% (P<0.05), and anti-GD1b antibodies in acute motor axonal neuropathy (AMAN) were 25% (P<0.05). Anti-GQ1b antibodies were detected in 54.5% in ataxia (P<0.05).*

Conclusion: *The results suggest that the average age of onset was older in the anti-ganglioside positive patients than in the negative patients. Anti-GM1 antibodies were highly expressed in AIDP and anti-GD1b antibodies were significantly expressed. In addition, the anti-GM1 antibody negativity was significantly associated with cranial nerve palsy and the anti-GQ1b antibodies were significantly associated with ataxia.*

Keywords: *Guillain-Barré syndrome, anti-ganglioside antibody , anti-GM1.*

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Introduction

In recent years, the relationship between anti-ganglioside antibodies and Guillain-Barré syndrome (GBS) has been subject to much research. It is generally believed that anti-ganglioside antibodies are closely related to GBS and variant subtypes of anti-ganglioside antibodies are often associated with different diagnoses[1-3], so early recognition of antibodies is helpful for diagnosis and treatment of GBS. However, other studies that do not find such a correlation[4].

However, the diagnostic use of anti-ganglioside antibodies may be limited because these antibodies are also closely related to other nervous system diseases, particularly multifocal motor neuropathy and chronic inflammatory demyelinating polyneuropathy [5-6].

GBS is a peripheral inflammatory and demyelinating autoimmune-related disease. Gangliosides-glycosphingolipids containing sialic acid-are known to play important roles in biological functions, such as cellular growth and immune reactions[7]. Antibodies to gangliosides have been found in autoimmune neuropathies, especially in GBS. Multiple experimental and clinical studies have shown anti-ganglioside antibodies play a role in the pathogenesis of GBS[1-3]. It is generally believed that pre-infection is recognised as the main triggering event, which activates the molecular mimicry to produce specific antibodies.

Patients with GBS develop anti-ganglioside antibodies, resulting in autoimmune targeting of peripheral nerve sites, leading to neural damage[2]. Anti-ganglioside antibodies are highly expressed in GBS, with approximately 45%-60% of GBS patients

presenting with anti-ganglioside antibodies in their sera[8]. According to clinical manifestations and electrophysiological criteria, GBS can be classified into acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), and other types, such as acute motor and sensory axonal neuropathy (AMSAN), and Miller Fisher syndrome (MFS). Studies have shown that different antibodies are associated with different clinical subtypes, such as anti-GQ1b in MFS and anti-GM1 in AMAN[1, 3]. In conclusion, antibodies play an important role in the pathophysiology of GBS and are closely related to clinical manifestations.

However, other studies have refuted this finding. Firstly, questions over the importance of these antibodies in GBS have been raised because anti-ganglioside antibodies are also observed in apparently healthy individuals and in patients with multifocal motor neuropathy and autism with a conduction block other than GBS[9-10], indicating that these antibodies are not specific to GBS. Secondly, studies have shown the clinical features of GBS and its subtypes are closely associated with some specific anti-ganglioside antibodies[1, 3]. However, not all studies report this correlation. For example, it is generally believed that anti-GM1 has a specific relationship with AMAN, but in a study on 162 GBS patients, anti-GM1 is related to AIDP[4].

In conclusion, anti-ganglioside antibody not only occurs in axonal GBS but also in healthy individuals and other nervous system diseases, undermining its specificity.

In summary, there is a relationship between antibodies and GBS, but the conclusions of previous studies are not uniform. Researchers examining the relationship between antibodies and GBS in clinical expression have not yet reached a consensus. Overestimation of clinical benefit or underestimation of risk to the relationship between antibodies and GBS will have an impact on clinical judgment. To resolve this uncertainty, this study explores the expression of serum anti-ganglioside antibodies in patients with GBS and its relationship to clinical features.

Methods

Patients and standard protocol approvals, registrations

A total of 104 patients with GBS were retrospectively studied, and 49 patients who underwent anti-ganglioside antibody testing were analysed at Shenzhen People's Hospital from 2016 to 2018.

The clinical diagnosis of GBS was made based on the National Institute of Neurological Disorders and Stroke (NINDS) criteria[11].

Phenotypic data, including age, antecedent symptoms, clinical subtypes, cranial nerve involvement, presence of ataxia, pathologic reflex, and time to nadir were evaluated.

This study was approved by the Ethics Committee of Shenzhen People's University Hospital. Good clinical practice guidelines in accordance with the Declaration of Helsinki were followed, and the privacy of patients was protected, as all data was anonymised and de-identified.

Anti-ganglioside-antibody tests

All serum samples were obtained from patients within 4 weeks of symptom onset.

An enzyme-linked immunosorbent assay was used to detect IgG- and IgM-type antibodies against the gangliosides GM1, GM2, GM3, GM4 GT1a, GT1b, GD1a, GD1b, sulfatide, and GQ1b as described elsewhere[12].

The presence of different types of anti-ganglioside antibodies was analysed by researchers who were blinded to the clinical information of the patients.

Electrophysiology

All patients received a neuroelectrophysiological examination, including electrophysiology and electroneurography, 14 days after onset of clinical symptoms. Serial nerve conduction studies (NCS) were performed as described elsewhere[13-14].

After a diagnosis of GBS, electrophysiological experts checked the results of the electrophysiological studies for GBS. Electrophysiological records were retrospectively evaluated by three physicians, and patients were classified as AIDP or AMAN according to Ho's criteria[15]. Patients with equivocal, inexcitable, or normal conductions were placed into the "other subtypes" group.

Statistics

Statistical analysis was performed using SPSS version 13.0 software. The count data are expressed as percentages and quantitative data are expressed as mean±standard deviation.

Comparisons between groups were made using Pearson chi-square or Fisher exact tests for categorical data, and 1-way analysis of variance was used for quantitative data. $P<0.05$ was considered statistically significant for all comparisons.

Results

Various serum antibodies (IgM and IgG) against gangliosides were detected in the 49 patients with GBS. As seen in Figure 1, a wide distribution of various anti-ganglioside antibodies was shown among the patients who were anti-ganglioside antibody-positive. The most frequent was anti-GM1 (n=17, 34.7%), followed by anti-GQ1b (n=11, 22.4%), anti-GM2 (n=4, 8.1%), anti-GD1b (n=4, 8.1%), anti-sulfatide (n=4, 8.1%), anti-GM3 (n=3, 6.1%), anti-GT1b (n=3, 6.1%), anti-GD1a (n=2, 4.0%), anti-GM4 (n=1, 2.0%), anti-GT1a (n=1, 2.0%). IgM anti-ganglioside antibody was positive in 15 (30.6%) and IgG anti-ganglioside antibody was positive in 18 (36.7%) (Fig. 1).

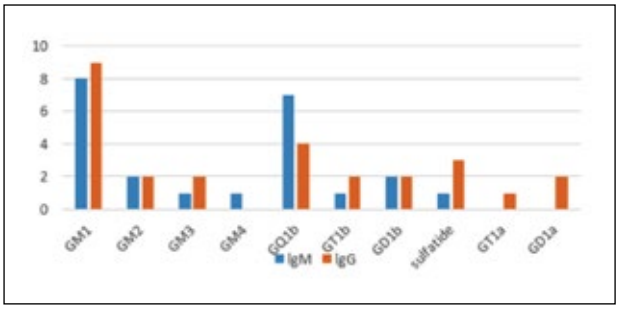

Figure 1: Expression of various IgM and IgG anti-ganglioside antibodies in GBS.

GM1, monosialotetrahexosylganglioside1; GM2, monosialotetrahexosylganglioside2; GM3, monosialotetrahexosylganglioside 3; GM4, monosialotetrahexosylganglioside 4; GQ1b, quadsialotetrahexosylganglioside 1b; GT1b, trisialotetrahexosylganglioside 1b; GD1b, disialotetrahexosylganglioside 1b; GT1a, trisialotetrahexosylganglioside 1a; GD1a, disialotetrahexosylganglioside 1a.

Table 1 shows the comparison of clinical features between groups of patients with anti-ganglioside antibody positivity and negativity. Forty-nine patients with GBS (male 23) were enrolled. Anti-ganglioside antibodies were positive in 33 (n=67.3%) and negative in 16 (n=32.7%). In general, there were no significant differences between the clinical features of antibody-positive patients and antibody-negative patients. The only significant difference observed was that the average age of onset was older in the anti-ganglioside antibody-positive group than in the antibody-negative group. In addition, the composition ratio of antecedent symptoms was statistically significant between the two groups.

Clinically, ganglioside-positive patients had antecedent infections (respiratory and gastrointestinal) more frequently. Cranial nerve palsy occurred in 18 patients with antibody positivity and in 9 patients with antibody negativity. Ataxia was observed in 8 antibody-positive patients and in 3 antibody-negative patients. Antibody positivity was expressed in 15 patients with AIDP, in 10 patients with AMAN, and 8 patients with AIDP.

Variable	Anti-ganglioside antibody positivity group (n=33) No. (%)	Anti-ganglioside antibody negativity group (n=16) No. (%)	p
Age (years)	48.8+16.1	35+16.1	P<0.05
Gender (men, %)	15 (45.5)	8 (50)	NS
Antecedent symptoms			P<0.05
Respiratory	15 (45.5)	8 (50)	NS
Gastrointestinal	2 (6.1)	6 (37.5)	NS
Others	2 (6.1)	0 (0)	NS
Unknown reasons	14 (42.4)	2 (12.5)	NS
Cranial nerve palsy	18 (54.5)	9 (56.3)	
Facial nerve palsy	5 (15.2)	3 (18.8)	NS
Oculomotor nerve palsy	10 (30.3)	2 (12.5)	NS
Abductor nerve palsy	7 (21.2)	2 (12.5)	NS
Other cranial nerve palsy	7 (21.2)	4 (25)	NS
Electrophysiological subtypes			
AIDP	15 (45.5)	6 (37.5)	NS
AMAN	10 (30.3)	2 (12.5)	NS
Other subtypes	8 (24.2)	8 (50)	NS
Pathologic reflex	2 (6.1)	0 (0)	NS
Ataxia	8 (24.2)	3 (18.8)	NS
Interval from the antecedent infection to disease-onset / days	5.2+6.5	5.8+6.8	NS
Interval from disease-onset to the most serious condition/days	6.4+5.7	5.6+4.3	NS
Interval from disease-onset to Antibody-detection/days	17.8+14.1	9.1+7.0	NS

Table 1: Comparison of clinical features between groups of patients with anti-ganglioside antibody positivity and negativity.

NS, not significant; AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy.

Table 2 shows the comparison of clinical characteristics between groups of patients with anti-ganglioside antibody positivity showing IgM and IgG. IgM anti-ganglioside antibodies were positive in 15 patients and IgG anti-ganglioside antibodies were positive in 18 patients. As seen in table 2, the clinical features included age, gender, antecedent symptoms, cranial nerve symptoms, ataxia, and electrophysiological categories. In general, there were no significant differences between the clinical features of the IgG anti-positivity patients and the IgM anti-posi-

tivity patients. NS, not significant; AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy.

Variable	lgM (n=15)	lgG (n=18)	*p*
Age (years)	51.2+21.0	46.7+11.0	NS
Gender (men, %)	7 (46.7)	8 (44.4)	NS
Antecedent symptoms			NS
Respiratory	7 (46.7)	8 (44.4)	NS
Gastrointestinal	0 (0)	2 (11.1)	NS
Others	1 (6.7)	1 (5.6)	NS
Unknown reasons	7 (46.7)	7 (38.9)	NS
Cranial nerve palsy	8 (53.3)	10 (55.6)	NS
Facial nerve palsy	3 (20)	2 (11.1)	NS
Oculomotor nerve palsy	5 (33.3)	5 (27.8)	NS
Abductor nerve palsy	3 (20)	4 (22.2)	NS
Other cranial nerve palsy	4 (26.7)	3 (16.7)	NS
Pathologic reflex	1 (6.7)	1 (5.6)	NS
Ataxia	4 (26.7)	4 (22.2)	NS
Electrophysiological subtypes			
AIDP	8 (53.3)	7 (38.9)	NS
AMAN	4 (26.7)	6 (33.3)	NS
Other subtypes	3 (20)	5 (27.8)	NS
Interval from the antecedent infection to disease-onset / days	4.6+5.2	5.7+7.6	NS
Interval from disease-onset to the most serious condition/days	8.6+7.2	4.8+3.5	NS
Interval from disease-onset to Antibody-detection/ days	17.4+16.0	12.7+12.5	NS

Table 2: Comparison of clinical characteristics among groups of patients with anti-ganglioside antibody-positivity showing IgG and IgM.

Table 3 shows the expression of various anti-ganglioside antibodies in different GBS subtypes. Anti-GM1 antibodies were observed in 9 patients with AIDP, in 7 patients with AMAN, and in 1 patient with other subtypes. The expression ratio of anti-GM1 antibody in the three subtypes was significantly different, being highly expressed in the AIDP (P=0.007) subtype. In addition, anti-GD1 antibodies were observed in 3 patients with AMAN, in 1 patient with other subtypes, and were not observed in the AIDP subtype. The expression ratio of the anti-GD1b antibody in the three subtypes was significantly different, being highly expressed in the AMAN (P=0.028) subtype.

NS, not significant; AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; GM1, monosialotetrahexosylganglioside 1; GM2, monosialotetrahexosylganglioside 2; GQ1b, quadsialotetrahexosylganglioside 1b; GD1b, disialotetrahexosylganglioside 1b.

Anti-ganglioside antibodies	AIDP (n=21)	AMAN (n=12)	Others (n=16)	p
GM1 (n=17)	9 (42.9)	7 (58.3)	1 (6.3)	P<0.05
GM2 (n=4)	1 (4.8)	2 (16.7)	1 (6.3)	NS
GQ1b (n=11)	5 (23.8)	1 (8.3)	5 (31.3)	NS
GD1b (n=4)	0 (0)	3 (25)	1 (6.3)	P<0.05

Table 3: Expression of various anti-ganglioside antibodies in different GBS subtypes.

Table 4 shows the relationship between anti-ganglioside antibodies and cranial nerve palsy. A total of 27 (55.1%) patients presented with cranial palsy. Among these patients, the presence of antibodies against GM1 was 22.2%, GM2 was 3.7%, GQ1b was 29.6%, and GD1b was 7.4%. Significant associations were only detected between anti-GM1 antibody negativity and cranial nerve palsy, as patients with anti-GM1 antibody negativity were more likely to have cranial nerve palsy.

Anti-ganglioside antibodies	yes (n=27)	no (n=22)	p
GM1	6 (22.2)	11 (50)	P<0.05
GM2	1 (3.7)	3 (13.6)	NS
GQ1b	8 (29.6)	3 (13.6)	NS
GD1b	2 (7.4)	2 (9.1)	NS

Table 4: Relationships between anti-ganglioside antibodies and cranial nerve palsy.

NS, not significant; AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; GM1, monosialotetrahexosylganglioside 1; GM2, monosialotetrahexosylganglioside 2; GQ1b, quadsialotetrahexosylganglioside 1b; GD1b, disialotetrahexosylganglioside 1b.

Table 5 shows the relationship between the anti-ganglioside antibodies and ataxia. There were 11(22.4%) patients who presented with ataxia. The only significant difference observed was that anti-GQ1b antibodies were more frequent in patients with ataxia.

Anti-ganglioside antibodies	yes (n=11)	no (n=38)	p
GM1	4 (36.4)	13 (34.2)	NS
GM2	0 (0)	4 (10.5)	NS
GQ1b	6 (54.5)	5 (13.2)	P<0.05
GD1b	0 (0)	4 (10.5)	NS

Table 5: Relationships between anti-ganglioside antibodies and ataxia.

NS, not significant; AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; GM1, monosialotetrahexosylganglioside 1; GM2, monosialotetrahexosylganglioside 2; GQ1b, quadsialotetrahexosylganglioside 1b; GD1b, disialotetrahexosylganglioside 1b.

Discussion

In this research, we investigated the expression of serum anti-ganglioside antibodies in patients with GBS and its relationship with clinical features. The results showed that the average age of onset was older in anti-ganglioside-positive patients than in the anti-ganglioside-negative patients. We also found that the composition ratio of antecedent symptoms was statistically significant between groups of patients with anti-ganglioside positivity and negativity. Clinically, ganglioside-positive patients had antecedent infections more frequently. Moreover, anti-GM1 antibodies were significantly expressed in AIDP, and anti-GD1b antibodies were significantly expressed in AMAN. In addition, the anti-GM1 antibody negativity was significantly associated with cranial nerve palsy and the anti-GQ1b antibodies were significantly associated with ataxia.

In our study, 33 (67.35%) patients presented with anti-ganglioside antibodies, with 15 being positive for multiple antibodies, which was consistent with previous studies[10, 16].

Previous studies have revealed that the frequency of anti-ganglioside antibodies ranged from 30-67%[8, 10, 16-20]. Researchers provided several explanations for these wide variations, such as differences in the method of analysis, timing of clinical sampling, frequency of antecedent infections, number of recruited patients, and definition of normal ranges[17]. The most frequently occurring antibody in our study was anti-GM1 (34.7%), which is consistent with another Korean study where the most commonly occurring antibody was anti-GM1[21], the significance of which is unknown. The presence of anti-ganglioside antibody subtypes varied in different studies. For example, Naik et al. from India reported the commonest antibody was GT1b[22], in contrast to other studies that showed GD1a antibodies to be the most frequent[23]. In an earlier study, the same group reported that GM2 antibodies were the most common in children with GBS, while GM3 and GD1b antibodies were dominant in the AMAN subtype. It may be supposed that regional differences in the prevalence and etiology of antecedent infections determine the pattern of antibodies[24]. The average age of onset was 48.8+16.1 years for anti-ganglioside antibody-positivity and 35+16.1 years for antibody-negativity, which was a significant difference. We also found that ganglioside positive patients had antecedent infections (respiratory and gastrointestinal) more frequently. Previous reports had shown that antecedent infections may be associated with the production of anti-ganglioside antibodies[2]. It was proposed that infectious agents had antigenic epitopes similar to gangliosides, stimulating the body to produce antibodies with high affinity. The underlying pathogenesis of GBS was that antibodies produce a cross-reaction through molecular mimicry, leading to peripheral nerve immunological damage.

This could explain the higher proportion of antecedent infections in antibody-positive patients. Different types of antecedent infections have been reported, such as Campylobacter jejuni, EB virus, and Cytomegalovirus, of which Campylobacter jejuni was the most common, reported to occur in 30% of patients with GBS[25].

In our study, 8 out of 31 GBS patients presented antecedent infections with gastrointestinal symptoms, but surprisingly anti-gangliosides antibodies were positive in only 2 patients, which suggests that the occurrence and development of GBS might be related to different pathogenic mechanisms or might be related to organisms other than C. jejunum[3].

Moreover, Campylobacter jejuni infection is more common in adolescents than adults. Most of our patients were adults with relatively low levels of Campylobacter jejuni, which could be because the antibody-positive patients were older. However, it is regrettable that our study did not detect Campylobacter jejuni, as this makes it difficult to further clarify the relationship between age of onset, antecedent infection, and gangliosides antibodies in GBS patients. Further studies are required to explain these findings.

Although we found that IgG antibodies were more common than IgM antibodies in GBS patients, the difference was not significant. Generally, it was considered that IgM antibodies are mainly associated with chronic diseases, whereas IgG antibodies are typically found in acute forms[26]. Moreover, the IgM type was more common than IgG in patients with CIDP[27]. As a result, researchers speculated that the timing of antibody detection in GBS patients was the key. In our study, the interval from disease-onset to antibody-detection varied little

between IgG and IgM antibody patients. Our interest in anti-ganglioside antibodies in GBS was kindled following the report on IgM anti-ganglioside antibodies in multifocal motor neuropathy. IgM anti-ganglioside antibodies had considerable limitations in diagnosing specific diseases compared with IgG antibodies[28]. Several studies have evaluated the role of IgG anti-ganglioside antibodies as a diagnostic and pathogenic finding in axonal GBS (like AMAN)[29]. In our study, IgG anti-ganglioside antibodies presented at a rate of 38.9% in AIDP and 33.3% in AMAN, which was not significant. However, studies have also reported that patients with GBS after cytomegalovirus infection frequently had anti-GM2 IgM antibodies[30-32], and patients that had Mycoplasma pneumonia infections frequently had IgM, IgG, or both antibodies[33-34]. Some studies tested only IgG and others analysed both IgG and IgM antibodies[35-37]. Lack of consistency in different studies precluded comparison of ganglioside antibodies across various studies.

The correlation between AMAN and antibodies against GM1[38-39], GD1b[40-41] has been widely investigated. Table 3 shows the expression ratio of the anti-GD1b antibody was highly expressed in AMAN (P=0.028), but the expression ratio of the anti-GM1 antibody was highly expressed in AIDP (P=0.007), rather than in AMAN. Similarly, several studies failed to show a correlation between AMAN and anti-GM1[42]. One possible explanation is that, with the current electrodiagnostic criteria for AMAN and AIDP, normal values could be set differently in different laboratories, which might affect the electrophysiological classification. Another possibility is that the target molecules involved in AMAN were not only GM1 but also GD1b, GD1a, GalNAc-Gd1a, or ganglioside complexes[43-44].

Additionally, differences in detection methods, a small number of specimens, or geographical differences could also cause differences in the results. Furthermore, some research has shown that target molecules are rarely identified in AIDP patients. High expression of the GM1 antibody in the AIDP subtype might be only one result of antibody cross-reactivity, which was not specific. Previous studies indicate that specific anti-ganglioside profiles were associated with certain phenotypic appearances.

Although the presence of anti-ganglioside antibodies is supportive and sometimes useful, it should not be relied upon,[43] because the antibodies are merely the products of cross-reactivity, not a unique indicator of GBS. The frequency of cranial nerve involvement did not differ significantly between the antibody-positive and -negative groups. However, in the antibody-positive group of our study, the presence of the anti-GM1-antibody was correlated with the absence of cranial nerve involvement, which was similar to previous studies[21]. One possible explanation for this is that GM1 antibodies are mainly distributed in the spinal nerve roots, which is associated with motor nerve disorders, such as AMAN or AMSAN, but not with cranial nerve involvement. Some reports showed GQ1b antibodies were concentrated in optic nerve motor neurons and were associated with ophthalmoplegia, medullary paralysis, facial paralysis, and limb weakness, but we only detected 4 patients with ophthalmoplegia, 4 with medullary paralysis, and 2 with facial paralysis in our study. Instead, we found anti-GQ1b antibodies were significantly associated with ataxia in our study. Similar studies had also proved such results[45]. A study of sensitised rabbits with GQ1b experiment provided support for the close relationship between antibody titer and ataxia[46]. In addition, previous studies showed ataxia was closely associated with anti-GD1b antibodies; however, this was not reproduced in our study. The small number of patients recruited into the study might explain the discrepancy, but further research is required to verify these findings

In conclusion, the results suggest that the average age of onset was older in the anti-ganglioside positive patients than in the negative patients. Anti-GM1 antibodies were highly expressed in the AIDP subtype and anti-GD1b antibodies were also highly expressed. In addition, the anti-GM1 antibody-negativity was significantly associated with cranial nerve palsy and the anti-GQ1b antibodies were significantly associated with ataxia. However, the results of this study cannot be generalised, as the sample size was small and research on a larger scale may be required to validate our findings.

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