Autoimmune Gastrointestinal Dysmotility Associated Gastroparesis (AGID-G): seropositive versus seronegative phenotypes

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BACKGROUND

- Autoimmune gastrointestinal dysmotility (AGID) is a consequence of autoimmune autonomic neuropathy and is a known cause of gastroparesis.
- The diagnosis of AGID-associated gastroparesis (AGID-G) often includes the identification of a neuronal autoantibody in the presence of dysautonomia and gastroparesis (seropositive disease).
- There is growing awareness of seronegative AGID-G in which no autoantibody is able to be identified via currently available tests.

AIM OF STUDY

- The aim of this study is to explore differences in clinical presentation and response to treatment between seronegative and seropositive AGID-G patients.
  - Demographics
  - GI symptoms and diagnosis, in particular GI dysmotility-associated
  - Severity of gastroparesis on gastric emptying study (GES)
  - Need for supplemental nutrition support (jejunal enteral feeding or parenteral nutrition)
  - Autoantibodies identified
  - Immunosuppressive treatments tried and subjective symptom response to treatment

METHODS

- A retrospective study was conducted of 2,729 adult patients who underwent neuronal autoantibody testing.
- Gastroparesis was confirmed via >10% retention of test meal at 4 hours during egg-toast meal gastric emptying study (GES).
- A diagnosis of AGID-G was confirmed clinically by GI and/or neurology clinical documentation.
- Fischer's exact test and t-test were used. A p-value of ≤ 0.05 was considered statistically significant.

RESULTS

- 2,729 adult patients who underwent autoantibody testing, 172 (6.3%) had gastroparesis.
- 40 of 172 gastroparesis patients were diagnosed with AGID-G: 20 seropositive AGID-G and 20 seronegative AGID-G (Table 1).
- Seronegative patients were more likely to require nutritional support (PEG-J or TPN) compared to seropositive patients (55.0% vs. 20%, p = 0.048) (Table 1).
- Notably, seronegative patients were more likely to fail PEG-J feeding and require TPN compared to seropositive patients (40% vs. 5%, p = 0.02).
- There were no statistically significant differences regarding age at gastroparesis diagnosis, gender, % retained at 4 hours on GES, or immunosuppressive treatments tried or responded to.
- There was no statistically significant differences regarding specific antibodies within the seropositive AGID-G cohort (Table 2), immunosuppressive treatments tried or (Table 3), or response to immunosuppressive therapies (table 3).

Table 1: Comparison of seropositive and seronegative AGID-G

	Seropositive (n=20)	Seronegative (n=20)	p value
Gender			0.09
Female	14	19	
Male	6	1	
Age at gastroparesis diagnosis (mean yrs, SD)	43.7 (16.4)	37.7 (15.1)	0.24
GI dysmotility Dx			NS
Diarrhea	1 (5%)	1 (5%)	
Constipation	14 (70%)	15 (75%)	
Gastroparesis	20 (100%)	20 (100%)	
Rapid gastric emptying*	1 (5%)	1 (5%)	
CIPO/SB dysmotility	2 (10%)	1 (5%)	
Accelerated SB transit	1 (10%)	0 (0%)	
% retained at 4hr on GES (mean %, SD)	34.6% (31.7)	29.0% (25.6)	0.54
Severe (>35% retained)	6 (30%)	5 (25%)	
Nutritional support needed			
PEG-J	4 (20%)	11 (55%)	**0.048**
TPN	1 (5%)	8 (40%)	**0.02**
Treatments tried			
At least 1 immunosuppressive	6 (30%)	12 (50%)	0.11
IVIG	5 (25%)	10 (50%)	
Steroid	3 (15%)	5 (25%)	
Rituximab	2 (10%)	4(20%)	
Cellcept	2 (10%)	2 (10%)	
Apheresis	0 (0%)	1 (5%)	

* Rapid gastric emptying was noted on a second GES at a different timepoint to GES demonstrating gastroparesis

Table 2: Autoantibody frequency among AGID-G patients

Autoantibody Ab	Seropositive (n=20*)
NMDA	0 (0%)
P/Q-type voltage-gated calcium channel	2 (10%)
N-type voltage-gated calcium channel	3 (15%)
Neuronal acetylcholine receptor (N-AChR)	4 (20%)
Muscle acetylcholine receptor (M-AChR)	1 (5%)
Voltage-gated potassium channel	5 (25%)
Striational	4 (20%)
Ganglionic	1 (5%)
ANNA-1	1 (5%)
GAD65	2 (10%)

* individuals could be positive for more than one antibody

Table 3: Seropositive vs. seronegative AGID-G patients: Comparison of immunosuppressant treatments

	Seropositive (n=6)	Seronegative (n=12)	p-value
Treatments Tried			
Treated with IVIG	5 (83.3%)	10 (83.3%)	1.0
Responded to IVIG	2 (40% of treated)	4 (40% of treated)	
Treated with Steroid	3 (50%)	5 (50%)	0.74
Responded to Steroid	2 (66.7% of treated)	0 (0% of treated)	
Treated with Rituximab	2 (33.3%)	4 (40%)	1.0
Responded to Rituximab	0 (0% of treated)	1 (25% of treated)	
Treated with Cellcept	2 (33.3%)	2 (20%)	0.4
Responded to Cellcept	0 (0% of treated)	0 (0% of treated)	
Treated with Apheresis	0 (0%)	1 (10%)	1.0
Responded to apheresis	0	0 (0% of treated)	

SUMMARY

- Differences identified between seropositive and seronegative AGID-G groups:
  - Seronegative patients were more likely to require nutritional support (PEG-J or TPN, 55.0% versus 23.8%)
  - Seronegative patients were more likely to be treated with immunosuppressive therapy (50% versus 30%)
- Similarities identified between seropositive and seronegative groups:
  - Average age at gastroparesis diagnosis
  - Gender
  - GI dysmotility diagnoses and symptoms
  - % retained at 4hr on GES and frequency of severe gastroparesis on GES
  - Frequency of specific immunosuppression treatments tried
- Comparison of immunosuppressive treatment response:
  - Seropositive and seronegative groups were similar in regard to the number of patients treated with IVIG (83% in both groups), as well as positive symptomatic response to IVIG treatment (40% in both groups).
  - A trend of better response to corticosteroids in the seropositive group compared to the seronegative group was noted (66.7% versus 0% respectively, not statistically significant)
  - Although not statistically significant, 1 (25%, n=4) seronegative patient responded to rituximab compared to 0 (0%, n=2) seropositive patients.

CONCLUSIONS

- Seronegative AGID-G patients were more likely to require nutritional support via PEG-J enteral feeding and/or TPN compared to seropositive AGID-G patients, despite other clinical factors being similar between groups.
- These results are hypothesis-generating and may indicate 1) a more severe disease course/more severe symptomatology for the seronegative AGID-G phenotype or 2) treatment delay in seronegative disease until later in disease course when supplemental nutritional support is required.
- Providers need to be aware and vigilant of seronegative AGID-G, particularly given the high prevalence of enteral and parenteral nutritional support needs.
- These findings have significant clinical implications, and further research regarding the identification of diagnostic markers and effective treatment options is needed.