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Short Communication

Rituximab treatment in seronegative autoimmune autonomic neuropathy and autoimmune autonomic ganglionopathy: Case-report and literature review

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ABSTRACT

Background and purpose: Autoimmune autonomic ganglionopathy (AAG) is a rare disease with no well-established treatment. Until recently, AAG could be seropositive (50 to 60% of patients) or seronegative for ganglionic (α3-type) nicotinic acetylcholine receptor (Gα3NAChR) antibodies. In early 2018, the two forms of the disease were distinguished, separating seropositive from seronegative ones, designating this latter form "seronegative autoimmune autonomic neuropathy" (SAAN). Most described treatments are plasma exchange (PE) and intravenous immunoglobulin (IVIG). However in some cases with no or small benefit, other immunomodulatory therapies, such as rituximab have been reported. We report the case of a 24-year-old female patient successfully treated for SAAN with rituximab and steroids after IVIG and PE failure. We also provide a review of case-reports reporting rituximab treatment for both SAAN and AAG.

Methods: To identify articles reporting SAAN and AAG treatment with rituximab, we searched the PubMed database using the terms "autoimmune autonomic ganglionopathy", "autoimmune autonomic neuropathy" or "seronegative autoimmune autonomic neuropathy" and "rituximab".

Results: Including our patient, nine cases have been described in the literature (4 SAAN and 5 AAG). Rituximab had a significant positive effect in 2 out of 4 SAAN and all 5 AAG cases, used alone or in association with other etiologic treatments.

Conclusion: Our study suggests rituximab (alone or in association with other treatments) could provide efficacy in both SAAN and AAG when PE and/or IVIG are not effective enough.

1. Introduction

Autoimmune autonomic ganglionopathy (AAG) is a rare acquired disease, characterized by diffuse autonomic failure involving sympathetic, parasympathetic and enteric functions. Main symptoms include orthostatic hypotension (OH), anhidrosis, xerostomia, reduced lacrimation, mydriasis, urinary retention and gastrointestinal dysmotility (constipation mainly, ileus, vomiting, more rarely diarrhea). Onset of disease is generally acute or subacute and less commonly chronic (Vernino et al., 2009; Imrich et al., 2009; Muppidi, 2018; Koike et al., 2010a; Klein et al., 2003; Mazzeo et al., 2013). AAG is mainly idiopathic, but can also be due to paraneoplasic syndrome (especially in thymoma, lymphoma and small-cell lung cancer) or may be associated with an autoimmune disease (e.g. Sjögren syndrome) (Vernino et al., 2009; Gupta et al., 2015). Until recently, AAG was sometimes associated with ganglionic (α3-type) nicotinic acetylcholine receptor (Gα3NAChR) antibodies, which were found in 50 to 60% of patients (Gupta et al., 2015; Iodice et al., 2009a). However, in early 2018, Golden et al. proposed to distinguish these two forms of the disease, separating seropositive patients for Gα3NAChR antibodies from

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seronegative patients, designating this latter form “seronegative autoimmune autonomic neuropathy” (SAAN) (Golden et al., 2018). In the following, AAG refers to seropositive autoimmune autonomic ganglionopathy.

Due to the rarity of SAAN and AAG, there is no well-established treatment. To date, recommendations for treatment are based on case-reports (Gupta et al., 2015). The most frequently described treatments are intravenous immunoglobulin (IVIG) and plasma exchange (PE), which are often used as first-line therapy (Iodice et al., 2009b; Nishihara et al., 2015). Providing only poor or transient benefits in some cases, some patients remain dependent on therapy to maintain remission, and for this reason, other immunomodulatory therapies may be used (Nishihara et al., 2015). In recent years, rituximab has been used successfully (Gupta et al., 2015; Hollenbeck et al., 2011). We report here the case of a SAAN patient treated in our Department with rituximab as third-line treatment after unsuccessful IVIG and PE therapies. We also provide a review of case-reports published in literature reporting the use of rituximab for the treatment of SAAN and AAG, in order to assess the efficacy of this drug in both forms of the disease.

2. Methods

To identify articles reporting AAG and SAAN treatment with rituximab, we searched the PubMed database using the terms “autoimmune autonomic ganglionopathy” or “autoimmune autonomic neuropathy” or “seronegative autoimmune autonomic neuropathy”, associated with “rituximab”. We selected articles written in English or French. Our patient gave consent for us to publish her case. No ethics committee approval was required according to local legislation.

3. Results

3.1. Case-report

In February 2014, a 24-year-old woman was referred to our department for bilateral nonreactive mydriasis, dysuria, dysphagia and constipation. She had a history of mild asthma treated with on-demand bronchodilator, but no allergies.

At the end of January 2014, the patient had come back to France after travelling to Mexico and New York. Two weeks after her return, she had flu-like syndrome with fever and myalgia. Three days later, she presented to the emergency department of a peripheral hospital because of dysphagia, nausea, constipation, dysuria, headaches, pharyngitis and blurred vision due to bilateral nonreactive mydriasis. A blood test revealed thrombocytopenia (77,000.10^6/L) and elevated C-Reactive Protein (CRP) (69 mg/L). Fever and thrombocytopenia normalized spontaneously within two days, and CRP decreased over the same period. However, dysuria worsened and progressed to acute urinary retention, leading to urinary catheterization. The dysphagia, nausea, and constipation also worsened and oral food intake was no longer possible. At this point, the patient was referred to our hospital.

At admission, the patient complained of dizziness when upright, skin dryness, xerostomia, and anhidrosis and she had bilateral nonreactive mydriasis (with photophobia), ileus and dysuria requiring urinary catheterisation. Nasogastric intubation and aspiration was needed because of the ileus. She did not present consciousness alteration, cranial nerve dysfunction (except for the mydriasis and xerostomia), and sensory or motor deficit. Deep tendon and plantar reflexes were normal. Cerebral, spinal, chest, abdominal and pelvic imaging were normal and ruled out malignancy. Standard blood tests and autoimmune biological tests (including anti-DNA and anti-nuclear antibodies, rheumatoid factor, anti-HU antibodies and acetylcholine receptor antibodies) were negative. Infectious disease serologies (including HIV, botulism, Campylobacter) were unremarkable. Cerebrospinal fluid was normal (proteins = 418 mg/L, glucose = 2.8 mmol/L, lactate = 1.4 mmol/L, white blood cells = 0/mm^3). Gα3NAChR antibodies were < 0.05 nmol/L by radioreceptor assay (normal if < 0.05 nmol/L; MVZ Labor Volkmann, Karlsruhe, Germany).

The diagnosis of SAAN was retained. COMPASS 31 (Composite Autonomic Symptoms Score, providing an index of severity and distribution of autonomic dysfunction (Iodice et al., 2009a; Sletten et al., 2012)) was found to be 51.31/100. Eleven days after the onset of the symptoms (D11), IVIG was started at 2 g/kg/day for 5 days. The improvement in the patient's condition was mild and lasted only a few days, with a moderate decrease in xerostomia and skin dryness, but no improvement in ileus, dysuria or mydriasis. At the end of the treatment, the COMPASS 31 was 42.17/100. Considering the poor response to treatment, we decided to proceed with PE. A first PE was performed on day 27 and the patient was then given PE every second day for 6 further sessions. Three litres of plasma were removed and replaced with isotonic 4.0% human albumin solution at each PE. PE did not improve the patient's condition: ileus, dysuria and mydriasis remained unchanged, and the COMPASS 31 was 64.38/100. However, there was no longer orthostatic intolerance. Due to the severity of ileus, it was decided to switch to a third-line treatment with rituximab. The patient was given one dose of 1000 mg of Rituximab on day 54, and 4 days later, prednisone at a dose of 1 mg/Kg daily (i.e. 60 mg per day) was started. A further dose of 1000 mg of rituximab was administered on day 68. Symptoms improved in the days following the second rituximab administration: intestinal transit was restored, dysuria improved and the urinary catheter was no longer needed, photophobia diminished, as did xerostomia, although anhidrosis remained unchanged. Steroid dose was decreased slowly over 6 months and symptoms did not recur. The addition of pyridostigmine (60 mg per day) improved mydriasis and totally corrected dysuria. Three years after discontinuation of medication, there was no relapse, and the only remaining symptoms were anhidrosis and mild mydriasis, with no photophobia.

3.2. Case-report review

Six articles, published between 2009 and 2018 were identified in the literature search. Including our patient, 4 SAAN and 5 AAG cases have been described. The main characteristics of these patients are presented in Tables 1 and 2. Among SAAN cases, 2 were women, median age was 26 years [range 24–35], while among AAG cases, 3 were women and median age was 63 [range 47–74]. Main symptoms included sympathetic (OH, anhidrosis), parasympathetic (reduced lacrimation, xerostomia, mydriasis, urinary retention, impotence) and

Table 1
Description of SAAN cases reported in the literature.

Case	Age/Sex	Main symptoms
1 (Golden et al., 2018)	26/M	OH, urinary retention, impotence, nausea and vomiting, gastroparesis, 30 kg weight loss over 2 months.
2 (Golden et al., 2018)	26/F	OH, anhidrosis, dry mouth, left-sided Horner-syndrome, nausea, constipation, paresthesia of extremities, body aches
3 (Golden et al., 2018)	35/M	OH, anhidrosis, dry mouth, dry eyes, urinary retention, ileus, painful paresthesia
4[a]	24/F	Orthostatic intolerance, anhidrosis, dry mouth, mydriasis, urinary retention, ileus

F = Female, M = Male, OH = Orthostatic hypotension.
[a] Our patient is referred to as Case 4.

Table 2
Description of AAG cases reported in the literature.

Case	Age/sex	Main symptoms	Gα3NAChR antibodies titer at diagnosis (upper limit of normal)
5 (Imrich et al., 2009)	74/F	OH, anhidrosis, dry mouth, urinary dysfunction, mydriasis	1.44 nmol/L (0.05 nmol/L)
6 (Gupta et al., 2015)	63/M	OH with bradycardia, anhidrosis, dry mouth, urinary retention, impotence, mydriasis, constipation, nausea and vomiting, 4.5 kg weight loss	0.96 nmol/L (NA)
7 (Hollenbeck et al., 2011)	65/F	OH, anhidrosis, dry mouth, constipation, 9 kg weight loss over 2 years	2.63 nmol/L (NA)
8 (Benizri et al., 2017)	47/M	OH, dry mouth, dry eyes, mydriasis, urinary retention, impotence, constipation, nausea and vomiting, 8 kg weight loss over 1 year	1691.4 pM (100 pM)
9 (Dumitrascu et al., 2017)	61/F	OH, anhidrosis	1.30 nmol/L (0.02 nmol/L)

Gα3NAChR = Ganglionic (α3-type) Nicotinic Acetylcholine Receptor, F = Female, M = Male, OH = Orthostatic Hypotension, NA = Not Available.

enteric (ileus, abdominal pain, nausea and vomiting, diarrhea, constipation) dysfunction. Weight loss was also reported. Painful paresthesia and decreased sensation were reported in SAAN cases (Golden et al., 2018). In two AAG cases, the disease was associated with hematologic malignancy: in Case 6 (Gupta et al., 2015), a diffuse large B-cell lymphoma (DLBCL) was diagnosed 15 months after initiating mycophenolate mofetil (MMF) for AAG treatment, and in Case 7 (Hollenbeck et al., 2011), AAG was diagnosed in a patient with small lymphocytic lymphoma (SLL).

Treatment sequences of etiologic therapies of SAAN and AAG are reported in Tables 3 and 4.

PE was used in the 4 SAAN patients, with only a moderate benefit in 2 of them. It was used in 4 out of 5 AAG patients, in association with prednisone in one case and with rituximab and steroids in one other, with substantial effects, however benefits were transient. The most frequently improved symptom was OH.

IVIG, used alone in 3 SAAN patients and in one AAG patient, provided no or only a mild improvement in symptoms.

Azathioprine was used in association with prednisone in one SAAN patient. This association led to symptom improvement only when rituximab was added.

High dose steroids (IV methylprednisolone), used in 2 SAAN cases, showed efficacy.

MMF was used in only 2 AAG patients, without association. It was effective in one case, but had to be stopped because diffuse large B-cell lymphoma (DLBCL) was diagnosed (15 months after initiating MMF).

Rituximab was used in all cases, as a median third-line therapy [range: 1–6]. It was always used to treat SAAN or AAG, except in one AAG case (used to treat DLBCL in association with chemotherapy, it relieved AAG symptoms). In SAAN patients, rituximab improved symptoms in 2 out of 4 cases: in association with azathioprine and prednisone (previous treatment by azathioprine plus prednisone only was ineffective) in one case and in association with prednisone in one other case. In AAG patients, rituximab was effective in all 5 cases (in association with steroids in 2 cases and with DLBCL-chemotherapy in 1 other); however, in 2 cases, patients remained dependent on regular rituximab infusions to maintain benefit. When described (only in 2 SAAN and 2 AAG cases), the median rituximab dose was 2 g [range 1-2 g]. Rituximab was well tolerated without serious adverse effects, except in one AAG case: opsoclonus-myoclonus syndrome occurred, and required discontinuation of rituximab and introduction of steroids (Case 9 (Dumitrascu et al., 2017)).

The course of anti-Gα3NAChR antibody titers was available in 4 out of 5 AAG patients. Antibody titers were associated with the severity of

Table 3
Treatment sequences and response in SAAN patients.

Case	Treatment	Response
1 (Golden et al., 2018)	PE (7 sessions)	Minimal improvement of OH, nausea and vomiting
	Prednisone (20 mg/d) + azathioprine (50 mg/d)	No benefit
	IV methylprednisolone (1 g/d for 5 days)	Improvement of OH and urinary retention, relapse on discontinuation
	Prednisone (60 mg/d) + azathioprine (2 × 50 mg/d) + rituximab (1 dose of 1000 mg)	Improvement of OH and gastroparesis but relapse of symptoms one month after self discontinuation of prednisone and azathioprine
	IV methylprednisolone (1 g/d for 5 days)	Improvement of symptoms, then relapse 6 months later (lost to follow-up)
2 (Golden et al., 2018)	Prednisone (60 mg/d) + methotrexate (for pre-existing seronegative rheumatoid arthritis)	No benefit
	PE (5 sessions)	No benefit
	IVIG (3 days)	No benefit
	Rituximab (1 dose[a])	No benefit
	IVIG (0,5 g/kg every 2 weeks) + hydroxychloroquine (200 mg/d)	Minimal improvement of bowel function, recovery of parasympathetic functions at 1.5 year, improvement of anhidrosis at 3 years
3 (Golden et al., 2018)	PE (5 sessions)	No benefit
	IVIG	No benefit
	IV methylprednisolone (1 g/d)	Improvement of OH, urinary function and neuropathic pain
	Prednisone	Symptom relapse
	IV methylprednisolone (1 g once a week then up to 1.2 g every 5 days)	Improvement of OH, urinary function, improvement of anhidrosis at 3 years
	Rituximab (4 doses[a])	No benefit
4	IVIG (2 g/kg/d for 5 days) started 11 days after onset	Mild improvement of orthostatic intolerance, anhidrosis, dry mouth and vomiting, relapse within few days
	PE (8 sessions) started 1 month after onset	Recovery of orthostatic intolerance
	Rituximab (1000 mg, 2 doses) + prednisone (60 mg/d) started 2 months after onset	Recovery of bowel function, improvement of dry mouth, mydriasis and urinary function, no relapse upon discontinuation (3 years after symptom onset)

d = day, IV = Intravenous, IVIG = Intravenous Immunoglobulin, OH = Orthostatic Hypotension, PE = Plasma Exchange.
In Treatment column, onset refers to the onset of the SAAN symptoms.
In Response column, periods refer to time since treatment initiation.
[a] Precise dose not available.

Table 4
Treatment sequences and response in AAG patients.

Case	Treatment	Response	Gα3NAChR antibodies titer
5 (Imrich et al., 2009)	PE (10 sessions) + prednisone (25 mg/d) started 1 year after onset	Dramatic but transient (< 4 weeks) improvement of OH and anhidrosis	initially < 0.1 nmol/L, then increase (≈ 0.8 nmol/L then ≈ 1.3 nmol/L)
	Rituximab (4 infusions of 275 mg/m^2 over 4 weeks) + prednisone (100 mg/d lowered to 10 mg/d for 5 months) started 1.5 years after onset	Improvement of OH and anhidrosis for at least 42 weeks (time of follow-up)	≈ 0.8 nmol/l then slow decrease (≈ 0.5 nmol/L)
6 (Gupta et al., 2015)	Steroids + MMF (2 g/d)	Improvement of OH, recovery of urinary and bowel function at 3 and 6 months	0.17 nmol/L
	MMF (2 g/d every 2 days)	Asymptomatic after 5 months	NA
	Stop MMF, R[a]-CHOP + Bortezomib (6 cycles), then rituximab maintenance therapy (8 cycles[a]) for DLBCL	Asymptomatic for AAG 9 months after the last dose (without any medication)	undetectable 9 months after the last dose
7 (Hollenbeck et al., 2011)	Rituximab (4 cycles[a]) started 1.25 year after onset	Improvement of symptoms at 3 months but then aggravation 1 year after last cycle	1.02 nmol/L 1 year after last cycle
	PE (5 days) started 1 year after rituximab	Improvement of OH, recovery of dry mouth	0.62 nmol/L, then 1.87 nmol/L few months later
	Rituximab (every 2 months[a]) started 6 months after PE	Significant improvement of OH and anhidrosis	Decrease, then undetectable
8 (Benizri et al., 2017)	PE (5 days)	Significant improvement of the symptoms, but PE needed 1–2 days monthly to maintain the effect	NA
	PE (1–2 days monthly) + rituximab[a] + steroids (10 mg/d)	Total resolution of the symptoms, but treatment regimen continued to be needed 1 year after starting rituximab	NA
9 (Dumitrascu et al., 2017)	IVIG, MMF[a] or PE	Moderate or transient benefit	NA
	Rituximab (1 g, 2 infusions 2 weeks apart)	Improvement of symptoms, side effect: OMS	0.69 nmol/L

d = day, AAG = Autoimmune Autonomic Ganglionopathy, DLBCL = Diffuse Large B-Cell Lymphoma, IV = Intravenous, IVIG = Intravenous Immunoglobulin, MMF = Mycophenolate Mofetil, NA = Not Available, OH = Orthostatic Hypotension, OMS = Opsoclonus-Myoclonus Syndrome, PE = Plasma Exchange, R-CHOP = Rituximab, Cyclophosphamide, Doxorubicin, vincristine, and prednisone.
In Treatment column, onset refers to the onset of the AAG symptoms.
In Response column, periods refer to time since treatment initiation.
[a] Precise dose not available.

symptoms. Rituximab mildly decreased the antibodies in 1 case and made them undetectable in 2 cases. In the last case, the antibody titer was approximately halved after IVIG, MMF, PE and rituximab. The decrease was prolonged (at least several months) in 2 cases.

4. Discussion

To the best of our knowledge, this is the first review of case-reports assessing the efficacy of rituximab in SAAN and AAG. Rituximab is a chimeric monoclonal antibody that selectively depletes CD20+ B-cells, sparing other cell lineages (Iodice et al., 2009b). In the cases included in our review, rituximab was mostly used when PE or IVIG failed to treat SAAN or AAG, and was used on median as third-line therapy. The median dose of rituximab was 2 g in the 4 cases in which it was reported.

Until recently, SAAN was considered as a variant of seropositive AAG, SAAN was considered as a variant of seropositive AAG with few specificities regarding symptoms, and was assumed to respond to the same treatment (Koike et al., 2012; Sandroni et al., 2004). Furthermore, another form of acute autonomic neuropathy characterized by profound autonomic and sensory dysfunction, preserved motor function, and negative titer of anti-acetylcholine receptor antibodies, designated as acute autonomic and sensory neuropathy (AASN) have also been reported (Koike et al., 2010b). In early 2018, Golden et al. (2018) reported 6 cases of SAAN and observed key differences with AAG patients. Concerning symptom differences, Golden et al. reported a prominence of sympathetic impairment and sensory symptoms, and a lack of specific pupillary failure in SAAN compared to AAG. Concerning treatment, they concluded that immunomodulatory therapy in SAAN provided less benefit than in AAG, and that SAAN were more likely to respond to steroids (Golden et al., 2018). Despite some differences in clinical presentation, it is unclear whether SAAN and AASN should be, nosologically, clearly divided into independent categories (Golden et al., 2018; Koike et al., 2010b). Furthermore, for other authors, the clinical picture and the response to immunotherapy are comparable in SAAN/AASN and AAG (Sandroni et al., 2004; Tijero et al., 2018). In our review, SAAN cases are limited to those described by Golden et al. in addition to our patient. In our patient, orthostatic intolerance was mild and no sensory symptoms were present, while nonreactive mydriasis was present and ileus was the predominant symptom. Such a clinical presentation in seronegative AAG have been already described (Koike et al., 2012).

Our patient was treated concomitantly with rituximab and steroids. The improvement in her condition occurred few days after the second rituximab dose, i.e. > 15 days after initiating the daily steroids treatment. This chronology and the absence of symptom relapse after steroid discontinuation suggest rituximab efficacy. Among SAAN patients, rituximab was effective in 2 out of 4 cases (in association with another treatment in both cases). It should also be noted that in one case rituximab failed to provide a benefit, only a single dose was provided. In 2 others cases, steroids (high dose IV methylprednisolone) provided benefit.

In AAG cases, rituximab was effective in all 5 cases (alone or in combination with other treatments). In two cases, patients remained dependent on repeated rituximab infusions to maintain benefit. Antibodies were correlated with the severity of the symptoms and became durably undetectable with rituximab in 2 of the 4 patients evaluated (Gibbons and Freeman, 2009).

When rituximab is effective, it appears to act quickly, as the improvement of symptoms occurs within a short time after rituximab introduction. This could be an important advantage of rituximab, since the symptoms of SAAN and AAG may be severe, or even sometimes life threatening (Vernino, 2009). Furthermore, a long duration before effective treatment seems to be associated with more severe nerve damages, with irreversible sequelae as compared to a short time to effective therapy (Koike et al., 2012; Koike et al., 2013). Yet, Gα3NAChR assay cannot be performed routinely, and results may take a long time to become available and provide the diagnosis of SAAN or AAG. For our

patient, blood samples were sent from France to Germany and the results were obtained 5 weeks later. Therefore, switching promptly to a second-line therapy with rituximab and/or steroids, after unsuccessful therapy with IVIG or PE, should be considered.

The potentially severe side effects, such as development of progressive multifocal leukoencephalopathy are the major limitations of rituximab (Iodice et al., 2009b). In our review, rituximab was well tolerated, except in one case in which the patient developed OMS, a rare rituximab side effect.

Some limitations of our study deserve to be mentioned. A major limitation is the lack of precise details regarding the time from symptom onset to initiation of etiologic treatments and symptom outcomes, and the lack of precise rituximab dosage in some cases. Therefore, it may be difficult to conclude regarding the efficacy (or inefficacy) of treatment in these cases. Another major limitation is that in most cases (including ours), rituximab was given concomitantly with other etiologic treatments, and thus, the evaluation of its specific efficacy is limited. Furthermore, AAG and SAAN are usually subacute disorders with a monophasic onset and a possible partial spontaneous improvement (Mazzeo et al., 2013; Koike et al., 2010b). Therefore, treatment efficacy should be interpreted with caution. Finally, other limitations include the retrospective nature of the study, the small number of identified cases and the varying level of detail of the symptoms description in the case-reports.

In conclusion, our study suggests efficacy of rituximab (possibly associated with steroids or another etiologic treatment) in patients with limited or no improvement of symptoms after first-line therapy with IVIG or PE in AAG cases but also in SAAN cases. The main advantages of rituximab are its short duration of administration and its early and prolonged effect. This efficacy should be confirmed in further studies.

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Conflicts of interest

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MB collected the data. MB, GN and FBS wrote the first manuscript draft. All authors were involved in the care of the patient. All authors participated in the writing of the final manuscript and all authors approved final manuscript. FBS was responsible for the overall supervision of the present work.

References

Benizri, S., Agmon-Levin, N., Kitrey, N.D., Carter, D., Goshen, E., Sharabi, Y., 2017. Clinical problem solving: a tobacco merchant who can't Spit. Isr. Med. Assoc. J. 19, 786–791.

Dumitrascu, O.M., McKeon, A., Zuniga, L., Grill, M.F., Goodman, B.P., 2017. Opsoclonus-myoclonus syndrome during rituximab treatment for autoimmune autonomic ganglionopathy. Neurol. Neuroimmunol. Neuroinflam. 4, e376.

Gibbons, C.H., Freeman, R., 2009. Antibody titers predict clinical features of autoimmune autonomic ganglionopathy. Auton. Neurosci. 146, 8–12.

Golden, E.P., Bryarly, M.A., Vernino, S., 2018. Seronegative autoimmune autonomic neuropathy: a distinct clinical entity. Clin. Auton. Res. 28, 115–123.

Gupta, A., Harris, S., Vernino, S., Naina, H.V., 2015. Rituximab-based therapy and long-term control of autoimmune autonomic ganglionopathy. Clin. Auton. Res. 25, 255–258.

Hollenbeck, R., Black, B.K., Peltier, A.C., et al., 2011. Long-term treatment with rituximab of autoimmune autonomic ganglionopathy in a patient with lymphoma. Arch. Neurol. 68 Available at. http://archneur.jamanetwork.com/article.aspx?doi=10.1001/archneurol.2010.289 (Accessed 5 November 2018).

Imrich, R., Vernino, S., Eldadah, B.A., Holmes, C., Goldstein, D.S., 2009. Autoimmune autonomic ganglionopathy: treatment by plasma exchanges and rituximab. Clin. Auton. Res. 19, 259–262.

Iodice, V., Kimpinski, K., Vernino, S., Sandroni, P., Fealey, R.D., Low, P.A., 2009a. Efficacy of immunotherapy in seropositive and seronegative putative autoimmune autonomic ganglionopathy. Neurology 72, 2002–2008.

Iodice, V., Kimpinski, K., Vernino, S., Sandroni, P., Low, P.A., 2009b. Immunotherapy for autoimmune autonomic ganglionopathy. Auton. Neurosci. 146, 22–25.

Klein, C.M., Vernino, S., Lennon, V.A., et al., 2003. The spectrum of autoimmune autonomic neuropathies. Ann. Neurol. 53, 752–758.

Koike, H., Koyano, S., Morozumi, S., et al., 2010a. Slowly progressive autonomic neuropathy with antiganglionic acetylcholine receptor antibody. J. Neurol. Neurosurg. Psychiatry 81, 586–587.

Koike, H., Atsuta, N., Adachi, H., et al., 2010b. Clinicopathological features of acute autonomic and sensory neuropathy. Brain 133, 2881–2896.

Koike, H., Hashimoto, R., Tomita, M., et al., 2012. The spectrum of clinicopathological features in pure autonomic neuropathy. J. Neurol. 259, 2067–2075.

Koike, H., Watanabe, H., Sobue, G., 2013. The spectrum of immune-mediated autonomic neuropathies: insights from the clinicopathological features. J. Neurol. Neurosurg. Psychiatry 84, 98–106.

Mazzeo, A., Stancanelli, C., Leo, R., Vita, G., 2013. Autonomic involvement in subacute and chronic immune-mediated neuropathies. Available at: https://www.hindawi.com/journals/ad/2013/549465/, Accessed date: 12 November 2018.

Muppidi, S., 2018. Autoimmune autonomic neuropathies: time to look beyond autoimmune autonomic ganglionopathy. Clin. Auton. Res. 28, 7–8.

Nishihara, H., Koga, M., Higuchi, O., et al., 2015. Combined immunomodulatory therapies resulted in stepwise recovery in autoimmune autonomic ganglionopathy. Clin. Exp. Neuroimmunol. 6, 191–194.

Sandroni, P., Vernino, S., Klein, C.M., et al., 2004. Idiopathic autonomic neuropathy: comparison of cases seropositive and seronegative for ganglionic acetylcholine receptor antibody. Arch. Neurol. 61, 44–48.

Sletten, D.M., Suarez, G.A., Low, P.A., Mandrekar, J., Singer, W., 2012. COMPASS 31: a refined and abbreviated composite autonomic symptom score. Mayo Clin. Proc. 87, 1196–1201.

Tijero, B., del Pino, R., Pérez-Concha, T., et al., 2018. Seronegative and seropositive autoimmune autonomic ganglionopathy (AAG): same clinical picture, same response to immunotherapy. J. Neuroimmunol. 319, 68–70.

Vernino, S., 2009. Auton Neurosci. 146. pp. 1–2.

Vernino, S., Hopkins, S., Wang, Z., 2009. Autonomic ganglia, acetylcholine receptor antibodies, and autoimmune ganglionopathy. Auton. Neurosci. 146, 3–7.