Evidence-based guideline: Clinical evaluation and treatment of transverse myelitis

Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology

ABSTRACT

Objective: To assess the evidence for diagnostic tests and therapies for transverse myelitis (TM) and make evidence-based recommendations.

Methods: A review of the published literature from 1966 to March 2009 was performed, with evidence-based classification of relevant articles.

Recommendations: Level B recommendations: neuromyelitis optica (NMO)-immunoglobulin G (IgG) antibodies should be considered useful to determine TM cause in patients presenting with clinical acute complete transverse myelitis (ACTM) features. The presence of NMO-IgG antibodies (aquaporin-4–specific antibodies) should be considered useful in determining increased TM recurrence risk. Level C recommendations: in suspected TM, distinction between ACTM or acute partial transverse myelitis may be considered useful to determine TM etiology and risk for relapse (more common with APTM). Age and gender may be considered useful to determine etiology in patients presenting with TM syndrome, with spinal infarcts seen more often in older patients and more female than male patients having TM due to multiple sclerosis (MS). Brain MRI characteristics consistent with those of MS may be considered useful to predict conversion to MS after a first partial TM episode. Longer spinal lesions extending over >3 vertebral segments may be considered useful in determining NMO vs MS. CSF examination for cells and oligoclonal bands may be considered useful to determine the cause of the TM syndrome. Plasma exchange may be considered in patients with TM who fail to improve after corticosteroid treatment. Rituximab may be considered in patients with TM due to NMO to decrease the number of relapses. Level U recommendations: there is insufficient evidence to support or refute the efficacy of other TM therapies or the usefulness of ethnicity to determine the cause of a subacute myelopathy. Neurology® 2011;77:2128–2134

GLOSSARY

ACTM = acute complete transverse myelitis; APTM = acute partial transverse myelitis; CI = confidence interval; IgG = immunoglobulin G; MS = multiple sclerosis; NMO = neuromyelitis optica; OCB = oligoclonal band; TM = transverse myelitis.

Transverse myelitis (TM), an inflammatory lesion of the spinal cord, occurs in 1 (severe) to 8 (mild) cases/million per year.1–3 TM is usually accompanied by MRI signal abnormality in the spinal cord, CSF pleocytosis, or both. Typical manifestations and inclusion/exclusion criteria were outlined by the Transverse Myelitis Consortium Working Group in 20026 (table e-1 on the Neurology® Web site at www.neurology.org). The lesion typically spans multiple vertebral segments and is not radiologically or pathologically transverse; the term transverse has been retained because of the importance of a spinal sensory level in making the diagnosis.7

This guideline seeks to answer the following clinical questions:

For patients with myelopathy, which demographic, clinical, radiographic, and laboratory features are useful:
DESCRIPTION OF THE ANALYTIC PROCESS

A literature search of Medline was performed for relevant articles published from 1966 to March 2009, using the following key words: myelitis, transverse myelitis, Devic disease, neuromyelitis optica, diagnosis, prognosis, outcomes, MRI, and treatments. The search was limited to reports in humans and abstracts available in English. Subheadings were applied as appropriate. The exact search strategy employed is described in appendix e-1. A secondary search of review articles was done to find any missed citations.

We reviewed all abstracts; the full text of potentially relevant articles was subsequently reviewed by at least 2 committee members. We excluded review articles and case reports. At least 2 committee members independently rated each article for its class of evidence using the American Academy of Neurology diagnostic (questions 1 and 2), prognostic (question 3), or therapeutic (questions 4 and 5) classification of evidence schemes (appendix e-2). Differences between reviewers were resolved through discussion with a third reviewer. Recommendations were formulated and linked to the strength of the evidence using the scheme described in appendix e-3.

ANALYSIS OF EVIDENCE

The search yielded 136 articles. All articles were reviewed in their entirety. Sixty-five articles met inclusion criteria.

For patients with myelopathy, which demographic, clinical, and laboratory features are useful to distinguish TM from other causes of acute and subacute noncompressive myelopathy? Demographic features. We identified 2 retrospective cohort studies (Class III) (n = 33 and n = 79) that described demographic features of patients with inflammatory (idiopathic TM, postinfectious, systemic collagen vascular disease, and neuromyelitis optica [NMO]) or noninflammatory (spinal infarct) acute myelopathies (table e-2). 8,9 Both studies demonstrated that patients with spinal cord infarcts were older (mean age 52 years [first study] and 67 years [second study]) than patients with TM (mean age 31 years [first study] and 50 years [second study]). When data from both studies were combined, they showed patients with inflammatory myelopathy were more often women (68% women for TM due to multiple sclerosis [MS] [95% confidence interval (CI) 0.51–0.81] and 80% women for TM due to any inflammatory cause [95% CI 0.51–0.77]).

Conclusions. In patients presenting with acute myelopathy, age is possibly useful in identifying patients at higher risk for spinal cord infarcts, and female gender is possibly useful in identifying patients at higher risk for inflammatory myelopathies (2 Class III studies).

Clinical features. We did not identify studies describing an association between clinical features of myelopathy (such as the time of onset to maximal neurologic deficit) and the etiology of the myelopathy (myelitis vs other types).

Conclusions. There is insufficient evidence to determine whether clinical features of the myelopathy are associated with myelitis vs other myelopathies.

Laboratory features. Two Class III studies (n = 79 and n = 28), both retrospective cohort surveys, found CSF pleocytosis (>10 cells/mm³) to be present more often in inflammatory processes (86% [95% CI 60%–96%]) than in spinal cord infarct (0% [95% CI 0%–20%]). 8,9,10

Conclusions. For patients with subacute myelopathies, an elevated CSF leukocyte count (greater than 10 cells/mm³) is possibly useful in identifying patients with inflammatory myelopathies (including TM) as opposed to those with spinal cord infarcts (2 Class III studies).

For patients with myelopathy, which demographic, clinical, radiographic, and laboratory features are useful to determine the cause of the myelitis? When the diagnosis of TM is established, determining the cause of the myelitis is useful. The main etiologies of TM-like syndromes are MS, para-infectious myelitis, NMO, and myelitis due to systemic disease (such as systemic lupus erythematosus). However, even after several years of follow-up, 15% to 36% of patients cannot be given a more specific diagnosis than “idiopathic” TM. 11,12

Demographic features. Of 4 Class III retrospective cohort surveys, the 2 largest (n = 36,79)8,13 reported that more women than men are diagnosed with inflammatory myelopathies due to MS, but no gender association was found in these 4 studies in idiopathic TM (95% CI 0.23–0.61; see table e-2). 8,9,13,14 Only Class IV studies are available regarding the association between ethnicity and the cause of myelitis.15,16 When comparing various types of myelitis, we found 2 studies showing no significant age differences and 2 studies with insufficient data to assess age differences concerning idiopathic TM vs MS presenting as myelitis (table e-2).

Conclusions. For patients with myelopathy, demographic features are possibly not useful in distinguishing causes of myelitis (multiple Class III studies).

Clinical features. TM is commonly divided into 2 subgroups on the basis of the extent of spinal cord

1. To distinguish TM from other causes of acute and subacute noncompressive myelopathy?
2. To determine the cause of the myelitis?
3. To identify patients at increased risk for recurrence?
4. Alleviate acute attacks?
5. Prevent future attacks?
involvement: acute complete transverse myelitis (ACTM) and acute partial transverse myelitis (APTM). ACTM is an acute or subacute inflammatory process of the spinal cord causing symmetric moderate or severe loss of function distal to that level. APTM is incomplete or patchy involvement of at least one spinal segment with mild to moderate weakness, asymmetric or dissociated sensory symptoms (i.e., spinothalamic function lost but dorsal column function spared), and occasionally bladder involvement. We reviewed the evidence regarding the potential usefulness of distinguishing ACTM from APTM in determining the cause of TM.

We found no studies directly comparing the risk of MS development in patients who have APTM with that in patients who have ACTM. However, Class III evidence from multiple natural history studies of well-characterized patients (cerebral MRI negative) with APTM and those with ACTM demonstrate an increased risk of MS development in the former group. Two studies of APTM (n = 30 and n = 9) demonstrated that transition to MS occurs at a rate of 10.3% (95% CI 4.1%–23.6%) whereas 2 studies of ACTM suggest a significantly lower rate of transition to MS of 0% to 2% (during approximately 5 years of follow-up of these conditions). One study characterized APTM as being rarely associated with NMO–immunoglobulin G (IgG) antibodies.

Conclusions. Patients with myelopathy who present as having APTM possibly have a higher risk of transition to MS vs those presenting as having ACTM (multiple Class III studies).

Radiographic features. Length of spinal cord lesion. We found 4 studies that address the length of MRI-detected spinal cord lesions in relation to the etiology of TM. Two of these studies, involving Japanese patients, directly compared the risk of developing NMO vs MS in patients with TM with longitudinally extensive lesions (defined as extending over at least 3 vertebral segments identified by standard strength [≥1.5 T] MRI scanning) with that of patients with TM with shorter lesions. In Japan, patients with optic neuritis or myelitis, regardless of lesion length, are classified as having “optic-spinal” MS. A large (n = 200) retrospective cohort study (Class III) suggested that Japanese patients with TM have a greater chance of manifesting the relapsing optic-spinal form (also fulfilling criteria for NMO) if they present with longitudinally extensive lesions rather than with short lesions (65% of patients who met NMO criteria were noted to have presented with longitudinally extensive lesions vs only 32% of patients with myelopathic MS, p = 0.001). Likewise, in another Class III retrospective cohort study Japanese patients with optico-spinal MS were more likely to have NMO defined by NMO antibody positivity (vs other types of spinal demyelinating disease, NMO antibody negative) if they had longitudinally extensive spinal lesions (p = 0.0036). Another retrospective cohort study (n = 22) of patients with short spinal cord involvement radiographically revealed a 4% (1/22) rate of developing NMO, and another prospective cohort study of 29 patients with a long spinal cord segment of myelitis radiographically revealed a high rate (38%) of NMO-IgG seropositivity and conversion to NMO or relapse.

Conclusions. The longitudinal extent of MRI lesions is possibly useful in determining the cause of TM (multiple Class III studies), specifically in distinguishing between NMO spectrum disorders and MS in patients with idiopathic TM.

MRIs demonstrating lesions typical of MS. One prospective Class II study of 26 patients with APTM provides evidence for the value of the presence of cerebral MRI lesions for predicting the development of MS. MS was diagnosed during 5 years of follow-up in 10/17 (59%) patients with any cerebral MRI lesions as compared with 1/9 (11%) patients without such lesions (p = 0.018).

A Class III retrospective cohort study of 15 patients with APTM also noted a high transition rate to MS in patients with cerebral MRIs typical for MS. In 2 Class III studies the transition rate to MS was 80% to 90% in patients with APTM followed over 3 to 5 years if cerebral MRIs showed 2 or more lesions typical for MS at presentation, vs 10%–11% transition rate to MS among patients presenting with normal cerebral MRIs. This finding is further supported by 4 Class III retrospective cohort studies of patients with APTM.

Despite the evidence that MRI lesions are predictive of MS, cerebral MRI lesions also occur fairly frequently in NMO. However, Barkhof cerebral MRI criteria are usually not satisfied in NMO, indicating that these lesions are not characteristic of MS.

Conclusions. In patients with TM, especially APTM, MS-like brain MRI abnormalities possibly indicate a higher risk of “conversion” to clinically defined MS (approximately 80% by 3–5 years after onset) (1 Class II study and multiple Class III studies).

Laboratory features. Autoantibodies. We found 1 Class I prospective study (n = 29) examining the predictive value of serum NMO-IgG positivity in identifying the etiology of TM. The presence of these autoantibodies (also termed aquaporin-4–specific autoantibodies) in patients with TM was associated with subsequent development of NMO or NMO
observed in a high likelihood of TM due to causes other
than MS if CSF pleocytosis was greater than 30 cells/
mm³ (seen in 35% of patients with myelitis, p = 0.005
by Fisher test). 8 A Class III case control study of
CSF of 71 patients with NMO vs patients with MS
showed a white cell count higher than 50/dL in 18 of
52 NMO cases, 28 of which had more than 10%
polymorphonuclear cells. 39

We found 8 Class III studies (30 to 79
patients) 8,9,12,13,18,39,40,41 using oligoclonal bands
(OCBs) to differentiate etiologies of TM (partial and
complete) and 1 Class II study (prospective
follow-up of 55 patients) 30 assessing the usefulness
of OCBs to predict transition to MS after APTM.
These studies found OCBs in 85%–90% of patients
with MS and in 20%–30% of patients with NMO or
vasculitis but none in patients with parainfectious
myelitis or spinal cord infarct. 8,9,26,39

CSF analysis for OCBs is possibly useful in
determining MS vs other causes of TM, specifically
for the diagnosis of MS vs NMO, spinal cord
infarct, vasculitis, and parainfectious and idiopathic
TM (1 Class II study and 8 Class III studies). Anal-
ysis of CSF for pleocytosis is possibly useful in distin-
guishing NMO from MS (1 Class III study) and MS
from all other causes of TM (1 Class III study).

For patients with myelopathy, which demograph-
ic, clinical, radiographic, and laboratory features
are useful to identify patients at increased risk for
recurrence?

Demographic features. No studies address the associ-
ation between demographic features of patients and
risk of TM recurrence.

Conclusions. There is insufficient evidence to deter-
mine whether demographic features are associated
with relapsing TM.

Clinical features. We found no studies that directly
compared the rate of recurrence in ACTM with that
in APTM. However, the rate of recurrence of idi-
opathic ACTM in the 5 years after onset is approxi-
mately 10%, 13 whereas the recurrence rate of
idiopathic APTM within 5 years is reported as ap-
proximately 40% (Class III evidence). 18

Conclusions. Relapse rates possibly differ in patients
with ACTM and patients with APTM (Class III evi-
dence from multiple studies), with relapse possibly
being more common in APTM.

Radiographic features. No information about recur-
rence was given in 2 Class III studies suggesting that
long spinal lesions may herald NMO. 21,22 Another
study (n = 29) prospectively found a high rate of
relapse (and development of NMO) in patients with
longitudinally extensive lesions (more than 3 seg-
ments) at presentation; however, the study did not
involve a group of patients with short lesions for
comparison. 23 One Class III study (n = 30) ad-
dressed whether multiple short lesions (vs a single
short lesion) increase risk of relapse or transition to
MS and found no predictive value. 18

Conclusions. Longer lesions on spinal MRI possibly
predict a higher risk of developing NMO; therefore,
some risk of recurrent TM is suspected, but the risk
relative to that from short lesions has not yet been
directly studied (Class III evidence from multiple
studies). There is insufficient evidence regarding the
value of multiple short lesions in predicting relapse
or transition to MS (1 Class III study).

Laboratory features. One prospective Class I study
found that the presence of aquaporin-4-specific auto-
antibodies predicts recurrence of TM or conversion
to NMO. 23 In this study, 44% of patients with TM
who were NMO positive had a relapse (myelitis or optic
neuritis) within 1 year as compared with 0% of the pa-
tients who were NMO negative (p = 0.012). Antinu-
clear antibodies were more frequent in the group with
relapses (25%) as compared with the group without re-
lapses (12%), but the difference was not significant.
The presence of antibodies to SSA/Ro antigen (60 kD
and 52 kD polypeptides complexed with Ro RNAs)
was also predictive of relapses (myelitis) after TM in
75% to 77% of patients in 1 Class III retrospective
cohort study (n = 25) (p = 0.047). 22

Conclusions. The presence of NMO autoantibodies
probably predicts relapse in patients with TM (1
Class I study). There is insufficient evidence con-
cerning whether the presence of SSA antibodies pre-
dicts recurrence after a first episode of TM (1 Class
III study).

For patients with TM, which therapies alleviate acute
attacks? Steroids. Only Class IV evidence exists con-
cerning the utility of steroids in treating TM.

Conclusions. In patients with TM, there is insuffi-
cient evidence to determine the utility of corticoste-
roid therapy in alleviating TM attacks (Class IV studi-
es).

Clinical context. Despite the absence of evidence,
administration of high-dose IV methylprednisolone
(1 g daily for 3 to 7 days) is typically the first-treat-

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ment offered to hasten recovery, reduce disease activity, and restore neurologic function.

**Plasma exchange.** The American Academy of Neurology recently published an evidence-based guideline on the efficacy of plasma exchange for neurologic disorders, including TM. The guideline concluded: “Based on a single Class II study [reference e4] plasmapheresis is possibly effective for acute fulminant CNS demyelinating diseases (including…TM) that fail to respond to high-dose corticosteroid treatment. Because the study included subgroups of patients with [different] demyelinating diseases, it is not possible to determine if plasmapheresis is more or less effective in patients with [TM].”

We found no additional studies to warrant changing this conclusion.e5– e7

**Mitoxantrone.** An open-label study prospectively evaluated the risk for attack recurrence in patients with NMO using mitoxantrone (12 mg/m² monthly for 6 months and then every 3 months for 3 additional doses) (Class III, MRI and clinical outcomes well defined and considered objective). Despite treatment, 2 subsequent attacks occurred during the initial 5 months of therapy, 1 designated as severe and the other as moderate. Systematic and longitudinal clinical (Expanded Disability Status Scale) and radiographic (MRI) measures of disease activity demonstrated improvements in 4 of the 5 patients.

**Conclusions.** There is insufficient evidence to determine the efficacy of mitoxantrone in alleviating TM attacks (single Class III studies).

**Rituximab.** Two uncontrolled, open-label Class III studies evaluated the use of rituximab in a combined total of 26 patients with NMO meeting established diagnostic criteria.e9–e10 The majority of patients included in both studies had experienced relapses despite treatment with one or more immunotherapies prior to treatment with rituximab. In the first study.e9 6 of 8 patients were attack-free over the follow-up period (mean = 12 months), and the reported median attack rate (attacks/patient/year) fell from 2.6 to 0 (p = 0.0078). Two of the patients experienced a TM episode subsequent to rituximab treatment. In the second study,e10 which included 7 of the patients enrolled in the first study, the median annualized relapse rate decreased from 1.7 to 0 after treatment with rituximab (p < 0.001) during the median follow-up period of 19 months. Two patients died during the follow-up period, 1 during a brainstem relapse and 1 from suspected septicemia.

**Conclusions.** Rituximab is possibly effective in reducing TM attacks in patients with NMO (2 Class III studies).

**Other agents.** Case reports, small case series, and retrospective reviews have suggested potential benefits of a variety of other agents to abort TM attacks, promote functional recovery, or influence the future predilection of additional attacks.e13–e19

**Conclusions.** There is insufficient evidence to determine the efficacy of azathioprine, cyclophosphamide, and IVIg in alleviating TM attacks (Class IV studies).

**For patients with TM, which therapies prevent future attacks?** Many of the same Class III and IV studies mentioned above have addressed prevention of recurrent TM attacks.

**Conclusion.** There is insufficient evidence regarding the use of other immunosuppressive strategies to reduce the risk of future TM attacks.

**RECOMMENDATIONS**

In patients with suspected TM, distinction between ACTM or APTM may be considered useful to determine the etiology of TM and the risk for relapse (more common in APTM) (Level C).

Age and gender may be considered useful to determine etiology in a patient presenting with TM syndrome, with spinal infarcts seen more often in older patients and more female than male patients having TM due to MS (Level C). Due to considerable overlap between groups, patient demographic characteristics are not definitive in establishing the cause of myelopathy.

There is insufficient evidence to support or refute the usefulness of ethnicity to determine the cause of a subacute myelopathy (Level U).

Brain MRI characteristics consistent with those of MS may be considered useful to predict conversion to MS after a first episode of partial TM (Level C).

Longer spinal lesions extending over more than 3 vertebral segments may be considered useful in determining NMO vs MS (Level C).

NMO-IgG antibodies should be considered useful to determine the cause of TM in patients presenting with clinical features of ACTM (Level B).

CSF examination for cells and OCBs may be considered useful to determine the cause of the TM syndrome (Level C).

The presence of NMO-IgG antibodies (aquaporin-4–specific antibodies) should be considered useful in determining an increased risk of TM recurrence (Level B).

Plasma exchange may be considered in patients with TM who fail to improve after corticosteroid treatment (Level C). Rituximab may be considered in patients with TM due to NMO to decrease the number of relapses (Level C). There is insufficient evidence to support or refute the efficacy of other therapies (Level U).

**RECOMMENDATIONS FOR FUTURE RESEARCH**

The efficacy of acute therapies, aimed at rapid intervention in acutely declining patients, should be ex-
amined prospectively and should be distinguished from efficacy of long-term therapies aimed at prevention of relapse. These cohort studies should prospectively examine, over at least a 3-year period, the clinical features of partial and complete TM, the longitudinal extent of MRI lesions, the presence of NMO antibodies or other laboratory information, and the presence or absence of cerebral lesions typical of MS to predict prognosis for recovery and relapse risk. Discriminant function analysis should be used to determine which clinical features of idiopathic TM clearly differentiate that condition from MS with myelopathy.

Randomized trials of therapeutic interventions for TM, such as plasma exchange or immunosuppressants, should be performed using corticosteroid therapy as the gold standard for comparison and both recovery and relapse as outcomes to be analyzed.

AUTHOR CONTRIBUTIONS

Dr. Scott: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, study supervision. Dr. Frohman: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, study supervision, obtaining funding. Dr. De Seze: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis. Dr. Weinshenker: drafting/revising the manuscript.

DISCLOSURE

Dr. Scott has received funding for travel or speaker honoraria from, served on the speakers’ bureaus and scientific advisory boards of, and performed consultation work for Acorda Therapeutics Inc., Avanir Pharmaceuticals, Biogen Idec, Nokarxis, and Teva Pharmaceutical Industries Ltd.; served as an associate editor for BMC Neurology and has received research support from Biogen Idec, National Multiple Sclerosis Society, Novartis, Pittsburgh Foundation, and Teva Pharmaceutical Industries Ltd. Dr. Frohman has received funding for travel and/or speaker honoraria from Biogen Idec, Teva Pharmaceutical Industries Ltd., Genzyme Corporation, Abbott, Acorda Therapeutics Inc., and Bayer Schering Pharma; has served on speakers’ bureaus for Biogen Idec, Teva Pharmaceutical Industries Ltd., Bayer Schering Pharma, and Athena Diagnostics; and has served as a consultant for Biogen Idec, Teva Pharmaceutical Industries Ltd., Athena Diagnostics, Inc., Acorda Therapeutics Inc., and Abbott. Dr. de Seze serves on scientific advisory boards for and has received honoraria from Biogen Idec, LFB, Merck Serono, sanofi-aventis, and Bayer Schering Pharma, and serves on the editorial board of Revue Neurologique. Dr. Gronenbier serves as an editorial advisory board member of Neurorologie Now, serves on a speakers’ bureau for Boehringer Ingelheim, and receives honoraria from Boehringer Ingelheim and the American Academy of Neurology. Dr. Weinshenker serves on data safety monitoring boards for Novartis and Biogen Idec; serves on the editorial boards of the Canadian Journal of Neurological Sciences, the Turkish Journal of Neurology, and Multiple Sclerosis; has received research support from Genzyme Corporation and the Guthy-Jackson Charitable Foundation; and receives license royalties from RSR Ltd. for a patent re: Aquaporin-4 associated antibodies for diagnosis of neuromyelitis optica.

DISCLAIMER

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CONFLICT OF INTEREST

The American Academy of Neurology is committed to producing independent, critical, and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least three AAN committees, a network of neurologists, Neurology peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com.

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REFERENCES


Endorsed by the Consortium of MS Centers on October 19, 2011. The American Academy of Neurology is to be congratulated for thoughtfully assessing the current status of evidence-based information and for revealing the need for much work before credible algorithms can be applied to the treatment of this syndrome.