

Anti-Ro/SAA Autoantibodies Might Represent the Antineuronal Antibodies Responsible for Cerebellar Degeneration in Sjögren's Syndrome

Syuichi Tetsuka (✉ syuichi@jichi.ac.jp)

International University of Health and Welfare Hospital, 537-3, Iguchi, Nasushiobara, Tochigi, 329-2763, Japan. <https://orcid.org/0000-0003-2654-368X>

Tomohiro Suzuki

International University of Health and Welfare Hospital: Kokusai Iryo Fukushi Daigaku Byoin

Tomoko Ogawa

International University of Health and Welfare Hospital: Kokusai Iryo Fukushi Daigaku Byoin

Ritsuo Hashimoto

International University of Health and Welfare Hospital: Kokusai Iryo Fukushi Daigaku Byoin

Hiroyuki Kato

International University of Health and Welfare Hospital: Kokusai Iryo Fukushi Daigaku Byoin

Research article

Keywords: Anti-Ro/SAA autoantibodies, Cerebellar degeneration, Purkinje cell, Ro52/TRIM21, Sjögren's syndrome

Posted Date: November 17th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-106003/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background: Neurologic disorders are one of the most common extraglandular manifestations of Sjögren's syndrome (SjS). Central neurologic symptoms can appear in about 5% of patients with SjS. However, only a few reports of cerebellar degeneration have been reported, and the clinical features and pathologic mechanisms of cerebellar degeneration associated with SjS are unclear.

Patients and methods: We recently treated cerebellar degeneration in a patient with SjS. We analyzed the serum and cerebrospinal fluid (CSF) to detect anti-Ro/anti-SjS-related antigen A (SSA) and anti-La/anti-SjS-related antigen B (SSB) antibodies. We also searched the literature for previous case reports on SjS to evaluate the characteristics of cerebellar degeneration in patients with SjS and examined whether the Ro/SSA (Ro52/tripartite motif protein [TRIM]21) protein was expressed in murine cerebellum using immunohistochemistry.

Results: Although all patients were positive for anti-Ro/SSA antibodies, some patients were negative for anti-La/SSB antibodies. Anti-Ro/SSA antibodies were observed in both serum and CSF. Anti-Ro/SSA antibodies were negative in the CSF of SjS patients without central nervous system involvement. Cerebellar atrophy was observed, and sequelae remained in the majority of the patients. Autopsy findings indicated a selective loss of Purkinje cells. Ro52/TRIM21 expression was detected throughout murine brains, including the hippocampus, cerebral cortex, and cerebellum. High Ro52/TRIM21 expression was observed in Purkinje cells.

Conclusions: We described the characteristics of cerebellar degeneration in patients with SjS and Ro52/TRIM21 expression in Purkinje cells of murine cerebellar tissue sections. Thus, these outcomes indicated that anti-Ro/SSA autoantibodies were likely responsible for cerebellar degeneration in SjS.

Background

Sjögren's syndrome (SjS) is an autoimmune disease in which exocrine glands, the primarily salivary glands, are damaged. In addition to exocrine glands, SjS is known to cause damage to a wide variety of organs, including the skin, joints, nervous system, lung, kidney, and digestive tract [1]. In particular, peripheral and central neurologic symptoms can be evident in about 15% and 5% of patients with SjS, respectively [2]. In the past decade, central nervous system (CNS) involvement in SjS has been observed more commonly than initially suspected, with disorders that include encephalitis, cognitive disorders, meningitis, myelitis, and cerebellar degeneration. However, only a few reports of cerebellar degeneration have been described, and the clinical features and the pathologic mechanisms of cerebellar degeneration associated with SjS remain uncertain. Anti-Ro/anti-SjS-related antigen A (SSA) and anti-La/anti-SjS-related antigen B (SSB) autoantibodies are important for the classification of SjS during diagnostic workups [3]. Based on molecular weights, the Ro/SSA and La/SSB autoantibodies target three different cellular proteins, namely, Ro52 (also referred to as tripartite motif protein [TRIM]21), Ro60, and La48 [3]. However, an understanding of the molecular and pathologic mechanisms behind autoantibodies in CNS manifestations of SjS, including cerebellar degeneration, is needed.

We recently treated cerebellar degeneration in a patient with SjS. Serum and cerebrospinal fluid (CSF) were analyzed for the presence of anti-Ro/SSA and anti-La/SSB antibodies. We also performed a literature review to assess the clinical characteristics, diagnostic methods, and therapeutic strategies used in SjS patients with cerebellar degeneration. Moreover, the expression of autoantigens (potential autoantibody target sites) in murine cerebellar tissue sections was examined to elucidate the molecular and pathologic mechanisms of cerebellar degeneration in patients with SjS.

Patients And Methods

1.1. Patients

Written informed consents were obtained from the patients of these case presentation with the accompanying images.

Patient 1 (SjS with cerebellar degeneration). A 36-year-old male patient was admitted to our Neurology Department with progressive gait imbalance. The neurologic examination disclosed dysarthria, dysmetria in both legs, an ataxic gait, and inability to walk with a tandem gait. The Scale for the Assessment and Rating of Ataxia (SARA) score was 24.5. Laboratory tests included the measurement of serum anti-Ro/SSA and anti-La/SSB antibodies, which had high values of ≥ 1200 and 198 U/mL, respectively, and positive antinuclear antibodies results (1/80). Both the Schirmer's and Fluorescein tests were positive, indicating that the patient had dry eye. A salivary gland biopsy was performed, revealing a lymphocytic infiltration around the salivary gland duct (Fig. 1A, B). The CSF showed increased anti-Ro/SSA antibodies at 15.9 U/mL and negative anti-La/SSB antibodies (< 1.0 U/mL). This neurologic patient was diagnosed with SjS, according to the American-European Consensus Group criteria [4]. Intravenous methylprednisolone (1 g/day) was administered for 3 days, and maintenance therapy with oral methylprednisolone was continued for 4 months. In addition, he received intravenous immunoglobulin treatments twice during his hospitalization. Four months later, significant clinical improvement was evident with a SARA score of 12. After 1 year, brain magnetic resonance imaging (MRI) showed cerebellar atrophy (Fig. 1C), compared with the MRI obtained at the time of hospital admission (Fig. 1D).

Patient 2 (SjS with chronic inflammatory demyelinating polyradiculoneuropathy [CIDP]). A 53-year-old male patient was admitted to our neurology department with numbness and weakness in all limbs. Deep tendon reflexes were not present in the upper and lower extremities. Serum anti-Ro/SSA and anti-La/SSB autoantibodies were 26.5 and 24.5 U/mL, respectively. A lip biopsy showed lymphocyte infiltration around the salivary gland duct. A series of electromyographic examinations showed polyradiculoneuropathy with demyelination, consistent with the electrodiagnostic criteria of CIDP. CSF specimens showed increased total protein levels (96 mg/dL), and the presence of both anti-Ro/SSA and anti-La/SSB autoantibodies were negative (< 1.0 U/mL). Brain MRI did not reveal abnormalities, and the patient was diagnosed with SjS with CIDP.

2.2. Literature review

We conducted a literature review by searching PubMed from 1990 to 2019 for keywords “Sjögren's syndrome,” “cerebellar” or “cerebellum,” and “Purkinje.”

2.3. Immunohistochemistry

Normal 8-week-old C57BL/6N male mice were used in these studies. Animal experiments were approved by the Institutional Animal Experiment Committee of the Genostaff Co., Ltd., Tokyo, Japan, and complying with the Institutional Regulations for Animal Experiments and Fundamental Guidelines for the Proper Conduct of Animal Experiments and Related Activities in Academic Research Institutions under the Ministry of Education, Culture, Sports, Science, and Technology. Using immunohistochemistry, paraffin-embedded murine sagittal sections of brain tissue were de-paraffined with xylene and rehydrated using graded ethanol and PBS. Antigen retrieval was performed in a citrate buffer at pH 6 and microwave treatment. Endogenous peroxidase was blocked with 0.3% H₂O₂ in methanol for 30 min, followed by incubation with G-Block (Genostaff) and an avidin/biotin blocking kit (Vector). Sections were incubated with an anti-Ro52/TRIM21 rabbit polyclonal antibody (Affinity Biosciences) at 4 °C overnight and were then incubated with biotin-conjugated anti-rabbit Ig (Dako) for 30 min at RT, followed by the addition of peroxidase-conjugated streptavidin (Nichirei) for 5 min. Peroxidase activity was visualized using diaminobenzidine staining. The sections were counterstained with Mayer's hematoxylin (MUTO), dehydrated, and then mounted with malinol (MUTO).

Results

3.1. The characteristics of cerebellar degeneration in patients with SjS

There were 14 patients with previously reported SjS, including Patient 1 in our study, who also developed cerebellar degeneration [5–17]. The characteristics of cerebellar degeneration in patients with SjS are shown in the Table. The average age of onset was 48.9 ± 19.4 years. The male/female ratio was overwhelmingly female, with 3 males and 11 females. On brain MRI, cerebellar atrophy was observed in the majority of the patients as the disease progressed (12/14 cases). Regarding the neurologic findings, there were three main symptoms: ataxia (14/14 cases), nystagmus (6/14 cases), and dysarthria (10/14 cases), suggesting cerebellar disturbances. A few patients had been diagnosed with SjS (2/14 cases), and many patients presented with cerebellar degeneration as the first manifestation of SjS, as in Patient 1 of our study. In many case reports, steroid or immunosuppressive therapies were provided, and despite the relatively good therapeutic responses to this type of therapy, sequelae remained in 11 of these 14 patients, including in Patient 1 in our study. In the majority of patients, cerebellar atrophy was observed after the onset of neurologic symptoms (12/14 cases). Interestingly, Nanri et al. reported on one SjS patient with cerebellar degeneration found on autopsy [12]. This patient had a selective loss of Purkinje cells, no apparent degenerative changes in the efferent pathways, such as the dentate or vestibular nuclei, and no prominent inflammatory reaction (Fig. 2).

The most notable finding in this literature review was the positive rate of autoantibody detection (Table). Although anti-Ro/SSA antibodies in the serum were positive in all patients, anti-La/SSB antibodies in the serum were negative in 5 of 14 patients [5, 10, 15–17]. Additionally, Patient 2 of our study, who had SjS with a peripheral neuropathy but no CNS involvement, was negative for both anti-Ro/SSA and anti-La/SSB antibodies in the CSF. These findings suggest that anti-Ro/SSA antibodies but not anti-La/SSB antibodies are involved in the pathology of SjS-related cerebellar degeneration. Therefore, we examined whether the Ro/SSA (Ro52/TRIM21) protein is expressed in the cerebellum of mice using immunohistochemistry.

3.2. Ro52/TRIM21 expression in the murine brain

We demonstrated that Ro52/TRIM21 expression was easily detected throughout the brain, including the hippocampus, cerebral cortex, and cerebellum (Fig. 3A), and that the control antibody did not exhibit any specific staining patterns (Fig. 3B). Ro52/TRIM21 expression was clearly detected in the murine cerebellum using anti-Ro52/TRIM21 antibodies (Fig. 4A) compared with the negative staining using normal rabbit Ig (Fig. 4B). In particular, high Ro52/TRIM21 expression was observed in the cytoplasm of Purkinje cells (Fig. 4A). This observation suggests that Ro52/TRIM21-expressing cells in the cerebellum (Purkinje cells) are major targets for anti-Ro52/TRIM21. In addition, Ro52/TRIM21 expression were also detected in the cytoplasm of the neurons on the cortex (Fig. 5A) and the hippocampus (Fig. 5B), and high levels of staining were observed by anti-Ro52/TRIM21 antibodies in the cytoplasm of neurons in CA3 region of hippocampus on high magnification image (Fig. 5C).

Discussion

The most notable points regarding cerebellar degeneration in SjS found in this study were that 1) although anti-Ro/SSA antibodies were found in all patients, there were patients in whom anti-La/SSB antibodies were negative, 2) anti-Ro/SSA antibodies were observed in both the serum and CSF, 3) in the SjS patient without CNS involvement, anti-Ro/SSA antibodies were negative in the CSF, 4) cerebellar atrophy was observed after the onset of cerebellar degeneration in SjS patients, and sequelae remained in most cases, 5) a selective loss of Purkinje cells was found in the histologic sections of human brain from one SjS patient with cerebellar degeneration, 6) Ro52/TRIM21 expression was detected throughout the murine brain, including the hippocampus, cerebral cortex, and cerebellum, and 7) high Ro52/TRIM21 expression was observed in Purkinje cells.

In the literature review, we found that all patients had anti-Ro/SSA antibodies, but some of those patients were negative for anti-La/SSB autoantibodies. This finding was counter to studies showing that anti-La/SSB autoantibodies are usually present with anti-Ro/SSA autoantibodies in serum, while anti-Ro/SSA autoantibodies could be detected without the presence of anti-La/SSB autoantibodies, suggesting the latter autoantibodies are not associated with the pathophysiologic mechanism of cerebellar degeneration in SjS. Furthermore, anti-Ro/SSA autoantibodies were observed in both the serum and CSF of our patients but were negative in the CSF of the SjS patient without CNS involvement. It is essential to detect antineuronal autoantibodies in the CSF of patients with autoimmune diseases of the CNS. The presence of anti-Ro/SSA autoantibodies in the CSF suggests that there is a disruption of the blood-brain barrier, that autoantibody-mediated neuroinflammation is involved in the pathophysiologic mechanisms of CNS disease, and that an immune-mediated neurologic disease is likely [18].

Anti-Ro/SSA antibodies are typically described as being associated with SjS and have been shown to have differential actions by two different target proteins, Ro52/TRIM21 (52 kDa) and Ro60 (60 kDa), that are biochemically and immunologically distinct [19]. The seropositivity prevalence rates were approximately 70% for anti-Ro52/TRIM21 autoantibodies, 40% for anti-Ro60 autoantibodies, and 50% for anti-La/SSB autoantibodies, and additionally, 63.2% of SjS patients with anti-Ro52/TRIM21 autoantibodies in serum also had anti-Ro60 autoantibodies [3, 20]. Clinical findings have been shown to be different between patients with anti-Ro52/TRIM21 and anti-Ro60 autoantibodies [19]. The Ro52/TRIM21 gene is 8.8 kb in size, located on chromosome 11, and a cytoplasmic protein that belongs to the TRIM family. This protein is involved in protein ubiquitination, proinflammatory states (interleukin 2), and apoptotic mechanisms, is suggested to play an important role in the regulation of inflammatory responses, and is upregulated at sites of autoimmune inflammation [21]. According to one study, intrathecal production of anti-Ro52/TRIM21 autoantibodies was observed in SjS patients with CNS involvement [22]. In addition, Ro52/TRIM21 was recognized by anti-Hu antibodies, which are onconeural antibodies for paraneoplastic neurological syndromes, including paraneoplastic cerebellar degeneration [23]. Although these results suggest that the Ro52/TRIM21 protein is involved to a greater extent in SjS-related cerebellar degeneration compared with the Ro60 protein, to the best of our knowledge, the distribution of this protein in brain remains unknown. In this study, we demonstrated that Ro52/TRIM21 was expressed throughout the murine brain, including the hippocampus, cerebral cortex, and cerebellum. Moreover, because the histopathologic hallmark of autoimmune cerebellar degeneration is a severe loss of Purkinje cells [24], we might be able to confirm this point from the results of our immunohistochemistry analysis and previous autopsy case report [11]. Although the pathogenic mechanisms of autoantibodies against Ro/SSA in autoimmune disease has remained unclear, there is the hypothesis that anti-Ro/SSA antibodies might cause direct damage to cells as well as anti-Yo antibodies that are onconeural antibodies associated with paraneoplastic cerebellar degeneration [25, 26]. Regarding anti-Ro52/TRIM21 autoantibodies, some studies have reported that these autoantibodies can penetrate the cytoplasm and inhibit the function of the Ro52/TRIM21 protein, which is to negatively regulate proinflammatory cytokines and degrade Ro52/TRIM21 E3 ubiquitin ligase activity [27, 28]. Furthermore, since anti-Ro/SSA antibodies were identified in the CSF of the SjS patients with cerebellar degeneration, it is possible that the anti-Ro/SSA antibodies might attack Purkinje cells, reducing Purkinje cell functions and activities, and cause symptoms of neurologic degeneration, resulting in cerebellar atrophy. Several reports have shown the presence of serum anti-Ro/SSA autoantibodies in SjS patients with limbic encephalitis [9, 29]. We demonstrated that Ro52/TRIM21 was expressed in the neurons of the cortex and hippocampus, which might indicate that anti-Ro/SSA autoantibodies are involved in other CNS involvements in addition to cerebellar degeneration.

Conclusion

In this literature review and the analysis of our patients, we evaluated the characteristics of cerebellar degeneration associated with SjS. Our study demonstrated high Ro52/TRIM21 expression in the Purkinje cells on histologic sections of cerebellum. We can conclude that anti-Ro/SSA autoantibodies are the antineuronal antibodies involved in the cerebellar degeneration of SjS patients and that the finding of anti-Ro/SSA antibodies in CSF might serve as a useful biomarker for SjS-related CNS disease in the clinical setting. Additional studies are warranted to confirm these observations and clarify the molecular and pathologic mechanisms of Ro/SSA autoantibodies as antineuronal antibodies. Finally, determining how these autoantibodies cause CNS dysfunction is also needed.

Abbreviations

CIDP
Chronic inflammatory demyelinating polyradiculoneuropathy
CNS
Central nervous system
CSF
Cerebrospinal fluid
MRI
Magnetic resonance imaging
SARA
Assessment and Rating of Ataxia
SjS
Sjögren's syndrome
SSA
SjS-related antigen A
SSB
SjS-related antigen B
TRIM
Tripartite motif protein

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent for publication was obtained and is available upon request.

Availability of data and materials

The datasets are available from the corresponding author upon reasonable request.

Competing interests

The authors declare no conflicts of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

ST, TS, RH and HK developed the main conceptual idea and research design. ST and TO performed experiment and data acquisition. ST, RH, and HK analyzed the data. ST wrote the manuscript. ST, TO, and HK edited manuscript. All authors approved the final version of the manuscript.

Acknowledgement

The authors would like to thank the Genostaff Co., Ltd. for technical support of immunohistochemistry.

Authors' information (optional)

Affiliations

Department of Neurology, International University of Health and Welfare Hospital, Nasushiobara, Japan.

Syuichi Tetsuka, Tomohiro Suzuki, Tomoko Ogawa, Ritsuo Hashimoto, Hiroyuki Kato.

References

1. Fox RI. Sjögren's syndrome. *Lancet*. 2005 Jul 23-29;366(9482):321-31. [https://doi.org/10.1016/S0140-6736\(05\)66990-5](https://doi.org/10.1016/S0140-6736(05)66990-5)
2. Carvajal Alegria G, Guellec D, Mariette X, Gottenberg JE, Demis E, Dubost JJ, et al. Epidemiology of neurological manifestations in Sjögren's syndrome: data from the French ASSESS Cohort. *RMD Open*. 2016 Apr 20;2(1):e000179. <http://dx.doi.org/10.1136/rmdopen-2015-000179>
3. Jonsson R, Brokstad KA, Jonsson MV, Delaleu N, Skarstein K. Current concepts on Sjögren's syndrome - classification criteria and biomarkers. *Eur J Oral Sci*. 2018 Oct;126 Suppl 1:37-48. <https://doi.org/10.1111/eos.12536>
4. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al; European Study Group on Classification Criteria for Sjögren's Syndrome. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis*. 2002 Jun;61(6):554-8. <http://dx.doi.org/10.1136/ard.61.6.554>
5. Terao Y, Sakai K, Kato S, Tanabe H, Ishida K, Tsukamoto T. Antineuronal antibody in Sjögren's syndrome masquerading as paraneoplastic cerebellar degeneration. *Lancet*. 1994 Mar 26;343(8900):790. [https://doi.org/10.1016/S0140-6736\(94\)91864-3](https://doi.org/10.1016/S0140-6736(94)91864-3)
6. Owada K, Uchihara T, Ishida K, Mizusawa H, Watabiki S, Tsuchiya K. Motor weakness and cerebellar ataxia in Sjögren syndrome—identification of antineuronal antibody: a case report. *J Neurol Sci*. 2002 May 15;197(1-2):79-84. [https://doi.org/10.1016/S0022-510X\(02\)00034-5](https://doi.org/10.1016/S0022-510X(02)00034-5)
7. Wong S, Pollock AN, Burnham JM, Sherry DD, Dlugos DJ. Acute cerebellar ataxia due to Sjögren syndrome. *Neurology*. 2004 Jun 22;62(12):2332-3. <https://doi.org/10.1212/01.WNL.0000130347.69790.E8>
8. Ichikawa H, Ishihara K, Fujimoto R, Katoh T, Arai M, Kawamura M, et al. An autopsied case of Sjögren's syndrome with massive necrotic and demyelinating lesions of the cerebellar white matter. *J Neurol Sci*. 2004 Oct 15;225(1-2):143-8. <https://doi.org/10.1016/j.jns.2004.07.010>
9. Collison K, Rees J. Asymmetric cerebellar ataxia and limbic encephalitis as a presenting feature of primary Sjögren's syndrome. *J Neurol*. 2007 Nov;254(11):1609-11. <https://doi.org/10.1007/s00415-007-0596-6>
10. Milic V, Ostojic P. Cerebellar ataxia in a patient with primary Sjögren's syndrome after treatment with chloroquine. *Rheumatol Int*. 2008 Oct;28(12):1295-6. <https://doi.org/10.1007/s00296-008-0615-7>
11. Nanri K, Shibuya M, Taguchi T, Hasegawa A, Tanaka N. Selective loss of Purkinje cells in a patient with anti-gliadin-antibody-positive autoimmune cerebellar ataxia. *Diagn Pathol*. 2011 Feb 4;6:14. <https://doi.org/10.1186/1746-1596-6-14>
12. Kim MJ, Lee MC, Lee JH, Chung SJ. Cerebellar degeneration associated with Sjögren's syndrome. *J Clin Neurol*. 2012 Jun;8(2):155-9. <http://dx.doi.org/10.3988/jcn.2012.8.2.155>
13. Chen YW, Lee KC, Chang IW, Chang CS, Hsu SP, Kuo HC. Sjögren's syndrome with acute cerebellar ataxia and massive lymphadenopathy: a case report. *Acta Neurol Taiwan*. 2013 Jun;22(2):81-6. http://www.ant-tnsjournal.com/Mag_Files/22-2/006.pdf
14. Sharma R, Chilukuri V, Sarma AK, Gokhale S. Primary Sjögren's syndrome presenting as acute cerebellitis. *J Clin Neurosci*. 2014 Mar;21(3):508-9. <https://doi.org/10.1016/j.jocn.2013.04.019>
15. Farhat E, Zouari M, Abdelaziz IB, Drissi C, Beyrouti R, Hammouda MB, et al. Progressive cerebellar degeneration revealing Primary Sjögren Syndrome: a case report. *Cerebellum Ataxias*. 2016 Oct 19;3:18. <https://doi.org/10.1186/s40673-016-0056-0>

16. Maciel R, Camargos S, Cardoso F. Subacute Cerebellar Degeneration as the First Manifestation of Sjögren's Syndrome. *Mov Disord Clin Pract*. 2017 Apr 10;4(4):637-638. <https://doi.org/10.1002/mdc3.12487>
17. Heidary M, Alesaeidi S, Afshari K. Cerebellar degeneration in primary Sjögren syndrome. *BMJ Case Rep*. 2018 Jun 6;2018. <http://dx.doi.org/10.1136/bcr-2017-223952>
18. Shimizu F, Nishihara H, Kanda T. Blood-brain barrier dysfunction in immuno-mediated neurological diseases. *Immunol Med*. 2018 Sep;41(3):120-128. <https://doi.org/10.1080/25785826.2018.1531190>
19. Schulte-Pelkum J, Fritzier M, Mahler M. Latest update on the Ro/SS-A autoantibody system. *Autoimmun Rev*. 2009 Jun;8(7):632-7. <https://doi.org/10.1016/j.autrev.2009.02.010>
20. Garberg H, Jonsson R, Brokstad KA. The serological pattern of autoantibodies to the Ro52, Ro60, and La48 autoantigens in primary Sjögren's syndrome patients and healthy controls. *Scand J Rheumatol*. 2005;34(1):49-55. <https://doi.org/10.1080/03009740510017940>
21. Oke V, Wahren-Herlenius M. The immunobiology of Ro52 (TRIM21) in autoimmunity: a critical review. *J Autoimmun*. 2012 Aug;39(1-2):77-82. <https://doi.org/10.1016/j.jaut.2012.01.014>
22. Mégevand P, Chizzolini C, Chofflon M, Roux-Lombard P, Lalive PH, Picard F. Cerebrospinal fluid anti-SSA autoantibodies in primary Sjögren's syndrome with central nervous system involvement. *Eur Neurol*. 2007;57(3):166-71. <https://doi.org/10.1159/000098469>
23. Manley G, Wong E, Dalmau J, Elkon K, Posner J, Furneaux H. Sera from some patients with antibody-associated paraneoplastic encephalomyelitis/sensory neuronopathy recognize the Ro-52K antigen. *J Neurooncol*. 1994;19(2):105-12. <https://doi.org/10.1007/BF01306451>
24. Dalmau J, Rosenfeld MR. Paraneoplastic syndromes of the CNS. *Lancet Neurol*. 2008 Apr;7(4):327-40. [https://doi.org/10.1016/S1474-4422\(08\)70060-7](https://doi.org/10.1016/S1474-4422(08)70060-7)
25. Yoshimi R, Ueda A, Ozato K, Ishigatsubo Y. Clinical and pathological roles of Ro/SSA autoantibody system. *Clin Dev Immunol*. 2012;2012:606195. <https://doi.org/10.1155/2012/606195>
26. Greenlee JE, Clawson SA, Hill KE, Wood B, Clardy SL, Tsunoda I, et al. Anti-Yo antibody uptake and interaction with its intracellular target antigen causes Purkinje cell death in rat cerebellar slice cultures: a possible mechanism for paraneoplastic cerebellar degeneration in humans with gynecological or breast cancers. *PLoS One*. 2015 Apr 17;10(4):e0123446. <https://doi.org/10.1371/journal.pone.0123446>
27. Mallery DL, McEwan WA, Bidgood SR, Towers GJ, Johnson CM, James LC. Antibodies mediate intracellular immunity through tripartite motif-containing 21 (TRIM21). *Proc Natl Acad Sci U S A*. 2010 Nov 16;107(46):19985-90. <https://doi.org/10.1073/pnas.1014074107>
28. Espinosa A, Hennig J, Ambrosi A, Anandapadmanaban M, Abelius MS, Sheng Y, et al. Anti-Ro52 autoantibodies from patients with Sjögren's syndrome inhibit the Ro52 E3 ligase activity by blocking the E3/E2 interface. *J Biol Chem*. 2011 Oct 21;286(42):36478-91. <https://doi.org/10.1074/jbc.M111.241786>
29. Çoban A, Özyurt S, Meriç K, Mısırlı H, Tüzün E, Türkoğlu R. Limbic Encephalitis Associated with Sjögren's Syndrome: Report of Three Cases. *Intern Med*. 2016;55(16):2285-9. <https://doi.org/10.2169/internalmedicine.55.6222>

Tables

Table. The clinical manifestations of Sjögren syndrome patients with cerebellar degeneration from our literature review

Author	Year/Sex/Age	Dry eye/mouth	Labial gland biopsy	ANA	Anti-Ro/SSA	Anti-La/SSB	Ataxia	Nystagmus	Dysarthria	Cerebellar atrophy	Previous diagnosis of SjS*	Therapy
Terao Y [5]	1994/M/61	☒/☒	NP	☐	☐	☐	☐	☐	☐	☐	☐	Pre
Owada K [6]	2002/F/55	☒/☒	☐	☐	☐	☐	☐	☐	☐	☐	☐	Pre
Wong S [7]	2004/F/16	☒/☒	☐	☐	☐	☐	☐	☐	☐	☐	☐	Pre
Ichikawa H [8]	2004//F/69	☒/☒	☐	☐	☐	☐	☐	☐	☐	☐	☐	Pre
Collison K [9]	2007/F/56	☒/☒	☐	☐	☐	☐	☐	☐	☐	☐	☐	Pre IVIG
Milic V [10]	2008/F/65	☒/☒	☐	☐	☐	☐	☐	☐	☐	☐	☐	None
Nanri K [11]	2011/F/84	☒/☒	☐	☐	☐	☐	☐	☐	☐	☐	☐	IVIG
Kim MJ [12]	2012/F/46	☒/☒	☐	☐	☐	☐	☐	☐	☐	☐	☐	Pre HCQ
Chen YW [13]	2013/F/44	☒/☒	NP	☐	☐	☐	☐	☐	☐	☐	☐	Pre
Sharma R [14]	2014/M/64	☒/☒	NP	☐	☐	☐	☐	☐	☐	☐	☐	Pre CTX
Farhat E [15]	2016/F/30	☒/☒	NP	☐	☐	☐	☐	☐	☐	☐	☐	Pre CTX
Maciel R [16]	2017/F/36	☒/☒	☐	☐	☐	☐	☐	☐	☐	☐	☐	Pre CTX
Heidary M [17]	2018/F/22	☒/☒	☐	☐	☐	☐	☐	☐	☐	☐	☐	Pre CTX
Our case	2020/M/36	☒/☒	☐	☐	☐	☐	☐	☐	☐	☐	☐	Pre IVIG

*Whether the diagnosis of SjS had been made prior to the onset of cerebellar degeneration. Abbreviations: M: male; F: female; NP: not performed; ANA: antinuclear antibody; Pre: prednisolone; IVIG: intravenous immunoglobulin; HCQ: hydroxychloroquine; CTX: cyclophosphamide; R: remission; I: Improvement; S: stable; P: progression.

Figures

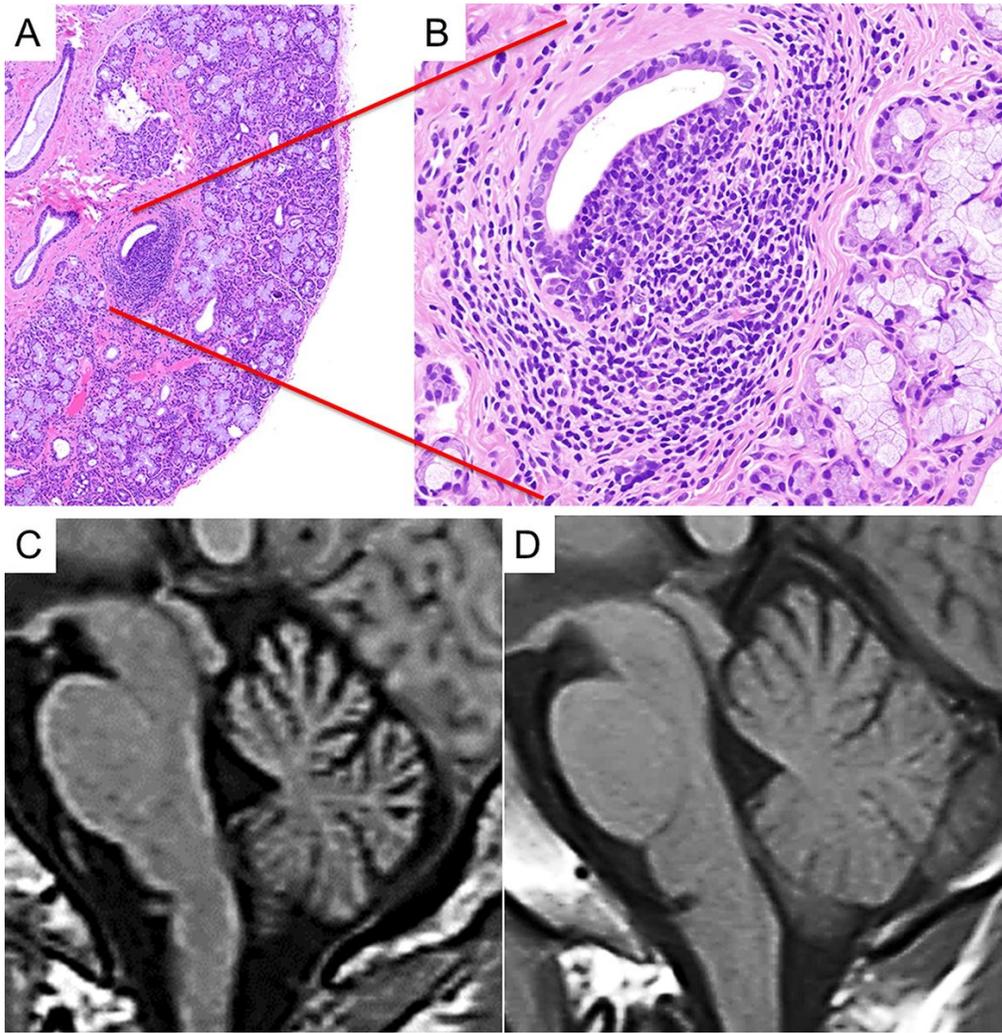


Figure 1
Patient 1 (SjS with cerebellar degeneration). (A and B) Photomicrographs of a salivary gland tissue section showing mild lymphocytic infiltration between the acini and glands, hematoxylin and eosin stain, magnification (A: $\times 40$, B: $\times 200$). (C and D) Sagittal views of the brain using magnetic resonance imaging (MRI) T1 sequences. (C) The follow-up MRI performed 1 year after the initial presentation revealed cerebellar atrophy. (D) The initial MRI was unremarkable.

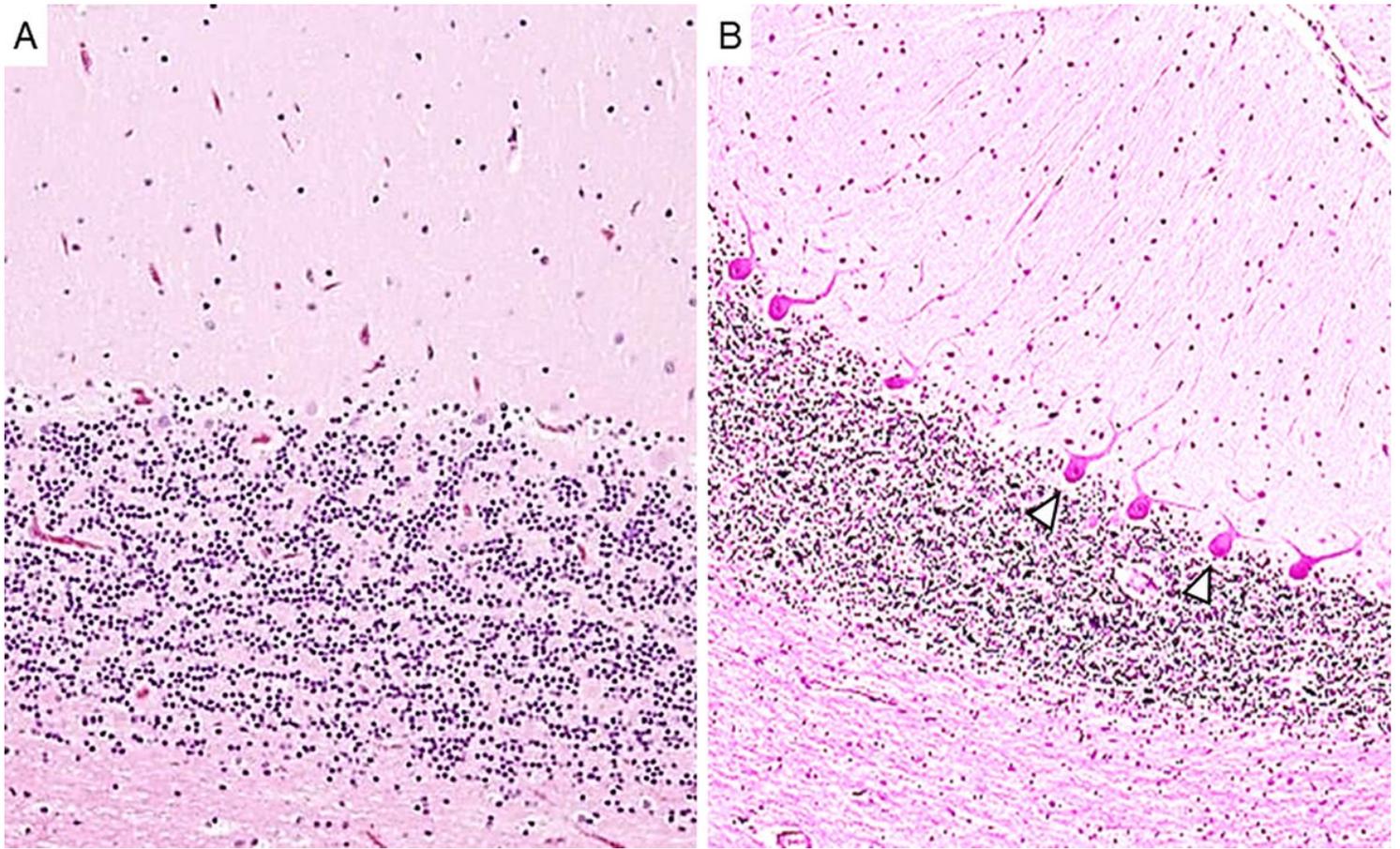


Figure 2

A selective loss of Purkinje cells in an SjS patient with cerebellar degeneration. The patient was an 84-year-old woman who presented with nystagmus, dysarthria, and ataxia in all limbs. Anti-Ro/SSA antibodies concentrations were >500 U/mL, and anti-La/SSB antibodies were 41.1 U/mL. Intravenous immunoglobulin therapy was moderately effective. The patient died of pneumonia at 85 years of age, and an autopsy was performed [11]. (A) A photomicrograph shows a mild-to-moderate decrease in the number of Purkinje cells in association with mild Bergman gliosis elsewhere in the cerebellar cortex. (B) This photomicrograph shows a normal human cerebellar tissue section with an appropriate number of Purkinje cells. Hematoxylin and eosin stain. The photomicrographs of tissue sections from this patient were reprinted and modified with permission from the publisher [11]. Arrowheads indicate Purkinje cells.

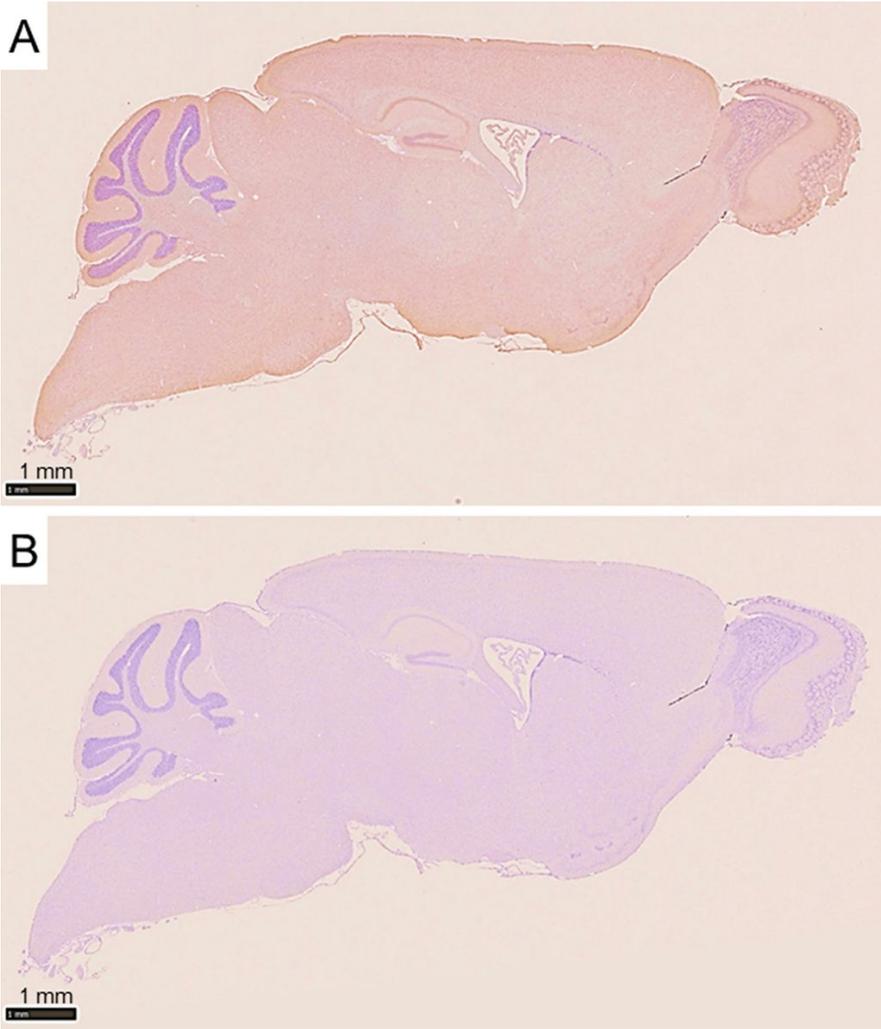


Figure 3
Photomicrographs of immunohistochemistry of a sagittal section of murine brain. (A) The section is stained with a commercially available anti-Ro52/TRIM21 antibody showing Ro52/TRIM21 expression throughout the entire brain, including the hippocampus, cerebral cortex, and cerebellum. (B) Negative control using an unrelated control antibody (anti-rabbit Ig) showing a lack of background staining. Counterstain: Hematoxylin.

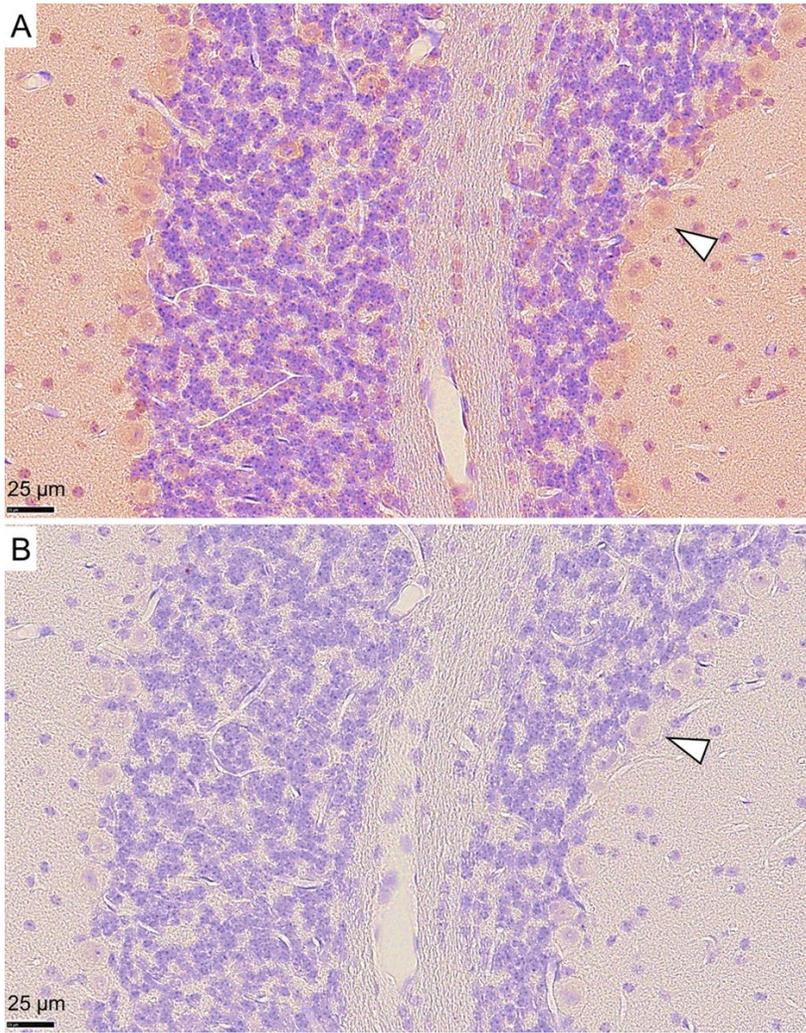


Figure 4

Photomicrographs of immunohistochemistry on murine cerebellar tissue sections. (A) Ro52/TRIM21 expression is shown using an anti-Ro52/TRIM21 antibody, but (B) is not present after staining with an anti-rabbit Ig (negative control). High Ro52/TRIM21 expression was observed in the cytoplasm of Purkinje cells. Arrowheads indicate representative Purkinje cells. Magnification: $\times 40$, Counterstain: hematoxylin.

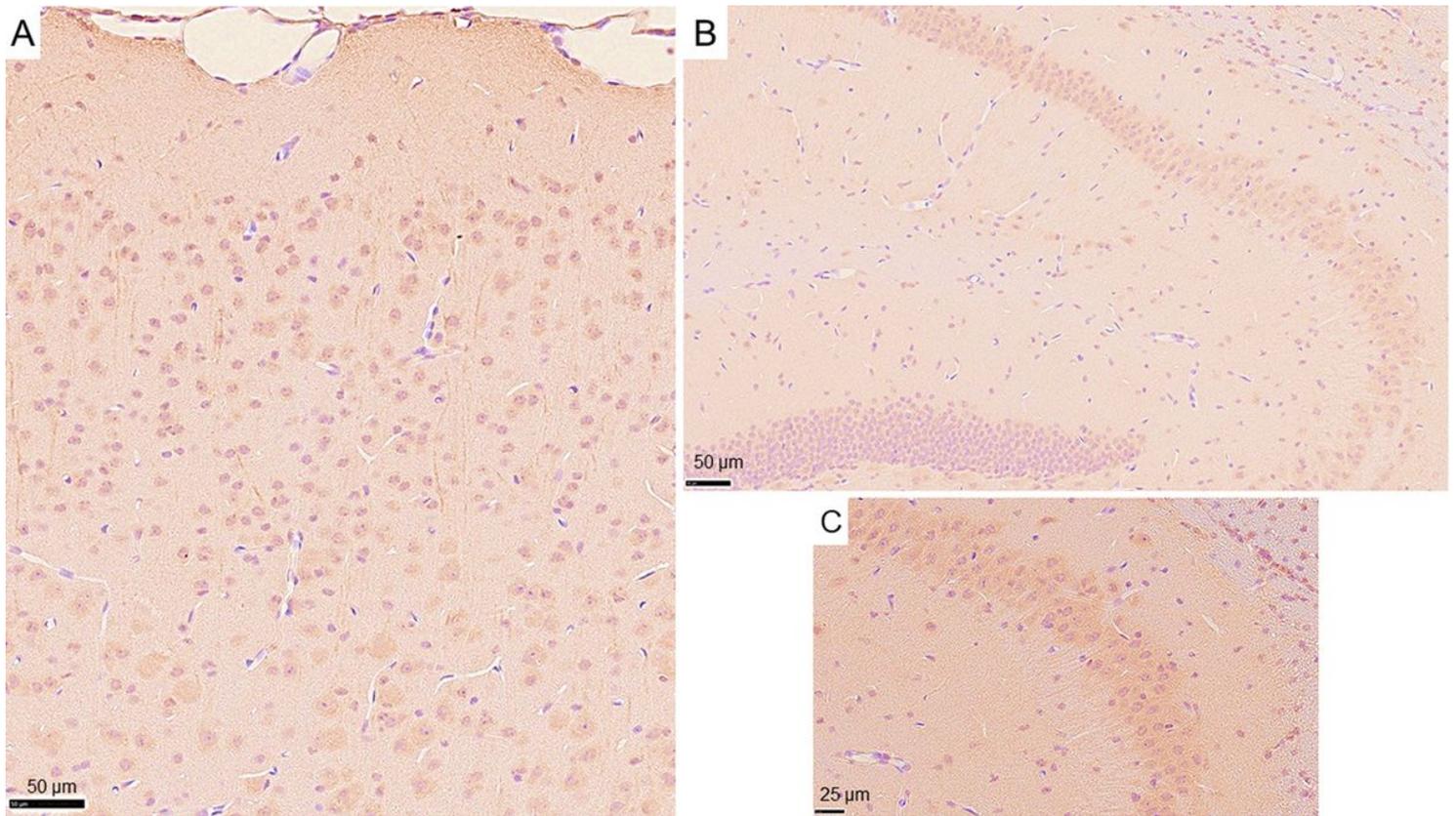


Figure 5
Photomicrographs of immunohistochemistry on other regions of the murine brain using the anti-Ro52/TRIM21 antibody. Cells that stained positively with the anti-Ro52/TRIM21 antibody were observed throughout (A) the cerebral cortex and (B) hippocampus (Magnification: $\times 20$). (C); High magnification image represent the CA3 region of hippocampus (Magnification: $\times 40$). Counterstain: hematoxylin.