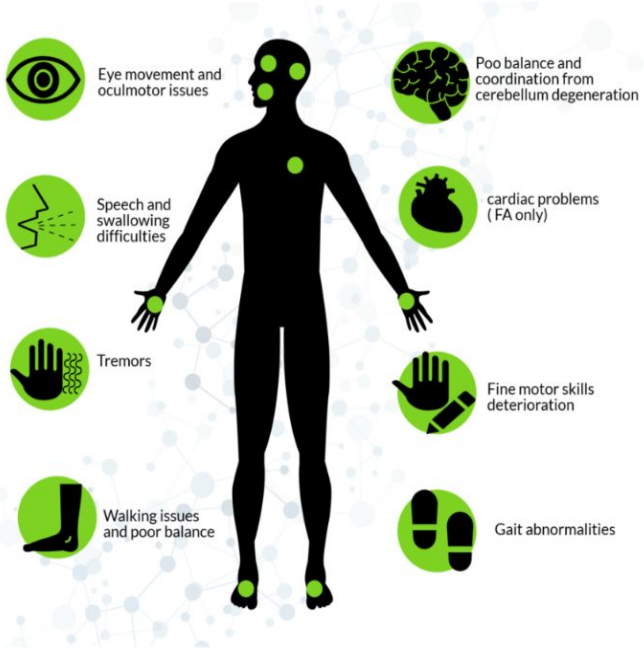
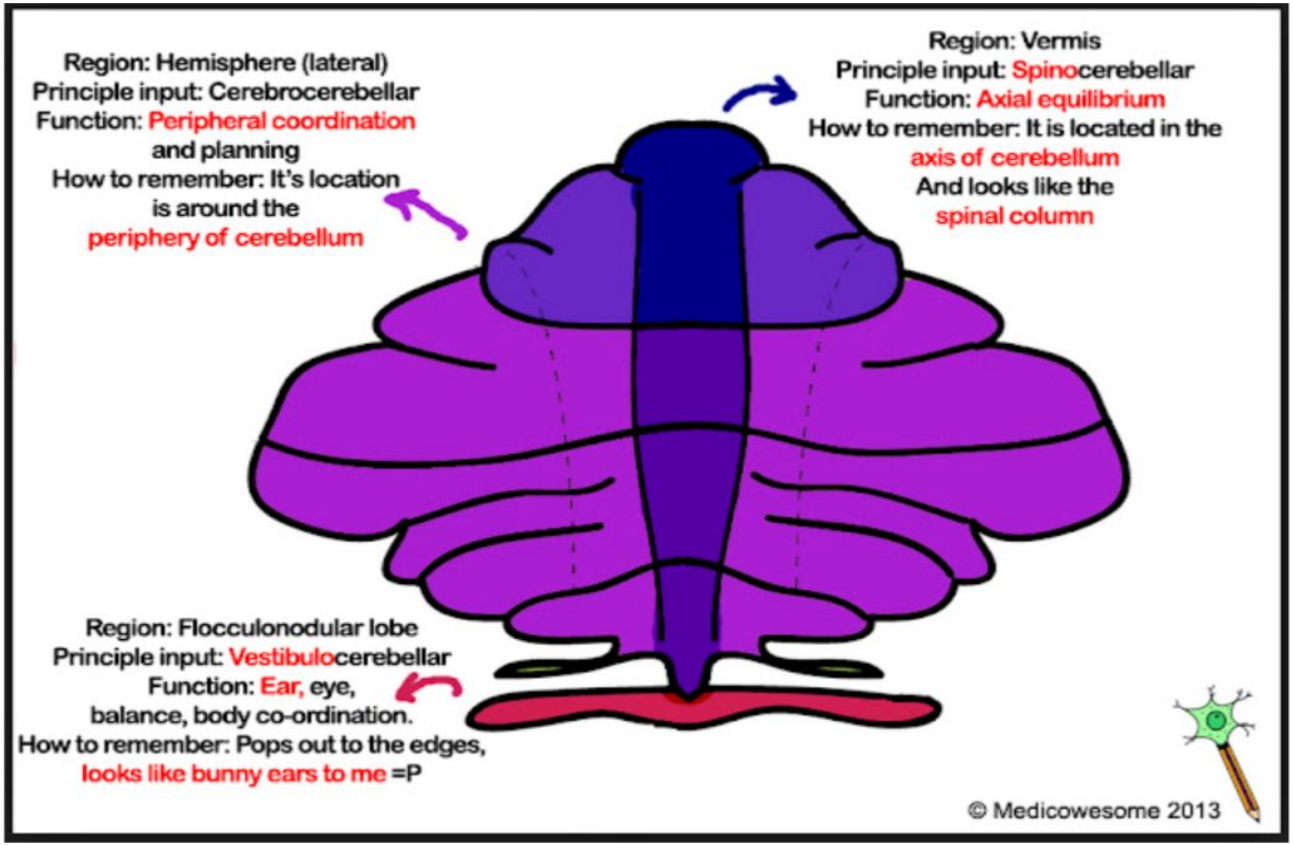
AUTOIMMUNE ATAXIA

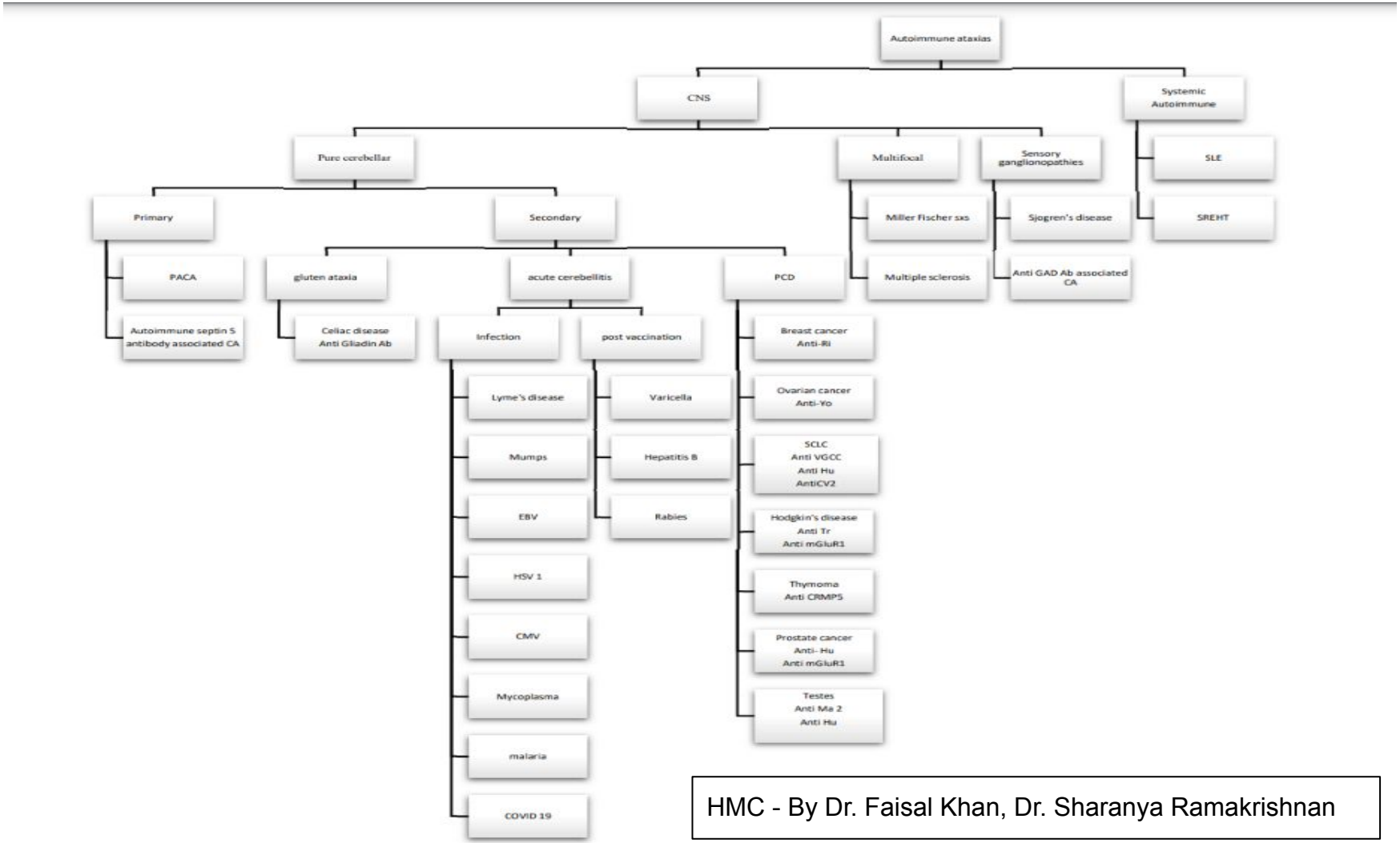
RAMYA TALANKI MANJUNATHA, MBBS

ATAXIA



- Ataxia is the term for a group of neurological diseases that affect movement and coordination.
- Ataxia affects people of all ages. Age of symptom-onset can vary widely, from childhood to late-adulthood.
- Ataxia symptoms vary from person to person. It can cause difficulty with walking and balance, hand coordination, speech and swallowing, and eye movements.


Region: Hemisphere (lateral)
Principle input: Cerebrocerebellar
Function: Peripheral coordination and planning
How to remember: It's location is around the periphery of cerebellum
Region: Vermis
Principle input: Spinocerebellar
Function: Axial equilibrium
How to remember: It is located in the axis of cerebellum And looks like the spinal column
Region: Flocculonodular lobe
Principle input: Vestibulocerebellar
Function: Ear, eye, balance, body co-ordination.
How to remember: Pops out to the edges, looks like bunny ears to me =P
© Medicowesome 2013



HMC - By Dr. Faisal Khan, Dr. Sharanya Ramakrishnan

PRIMARY AUTOIMMUNE CEREBELLAR ATAXIA

- Primary autoimmune cerebellar ataxia (PACA) are a group of patients with suspected IMCA in which neither a trigger nor any pathogenic neuronal antibodies have been discovered as yet.

- A task force was commissioned by the Society for Research on the Cerebellum and Ataxias (SRCA) in 2017 and they devised the diagnostic criteria for PACA.

- A clinical trial was conducted on 30 patients with PACA. Patients were treated with mycophenolate and monitored using MR spectroscopy of the cerebellar vermis. The study demonstrated that treatment with mycophenolate in patients with suspected PACA results in increased NAA/Cr area ratio of the cerebellar vermis as measured with MRS. Such increase is associated with clinical improvement.

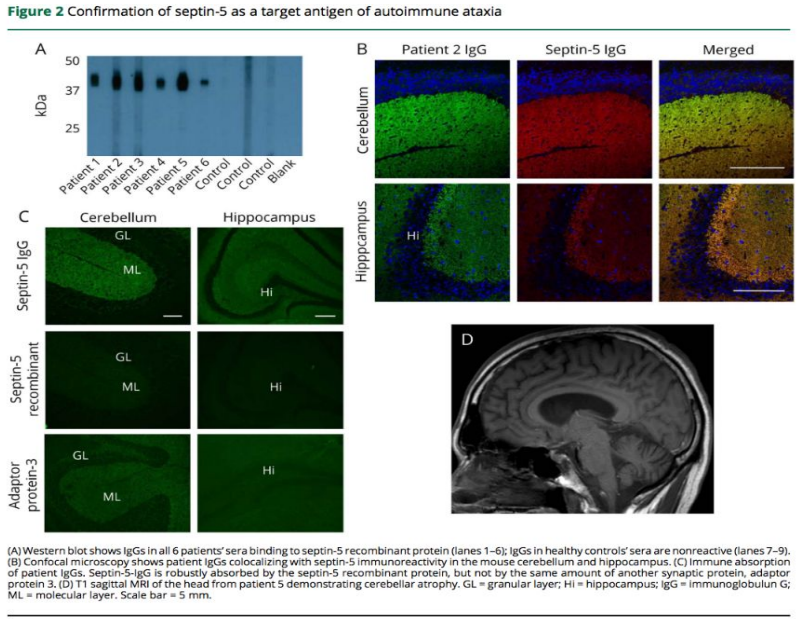

1. Predominantly subacute or acute pure cerebellar syndrome: gait ataxia that may be associated with variable degrees of limb incoordination, dysarthria, nystagmus, diplopia
2. MRI at presentation usually normal or may show primarily cerebellar vermian atrophy with (if available) reduced MR spectroscopy of the vermis.
Immune mediated ataxias with a known trigger factor: paraneoplastic cerebellar degeneration, gluten ataxia, post-infectious cerebellitis
Presence of well characterized neuronal antibodies directly involved in ataxia pathogenesis (e.g. DPPX, mGluR1, GABAbR)
treat accordingly
3. At least 2 of the following:
a. CSF pleocytosis and/or positive CSF restricted IgG oligoclonal bands
b. History of other autoimmune disorders or family history of autoimmune disorders in first degree relatives
c. Presence of antibodies that support autoimmunity but not yet shown to be either directly involved in ataxia pathogenesis or to be markers of ataxia with a known trigger (table 1)
consider immune modulation
4. Exclusion of alternative causes made by an experienced neurologist or ataxia specialist
PACA

Table 1

Some examples of autoantibodies observed in primary autoimmune cerebellar ataxia

1 Examples of autoantibodies associated with non-neurological autoimmune diseases that may raise suspicion of PACA	
Thyroid peroxidase, thyroglobulin	PACA, thyroid autoimmune diseases
Anti-SS_A (Ro), SS_B (La)	PACA, Sjogren's syndrome
2 Examples of autoantibodies reported only in a few patients with ataxia, thus significance in the context of ataxia is less well characterized but their presence may raise suspicion of PACA	
Autoantibody	*Clinical features*
Anti-Sj/ITPR-1	Variable clinical course
Anti-Ca/ARHGAP26	Variable clinical course. Association with neoplasm reported
Anti-MAG	Chronic gait ataxia and neuropathy. Ataxia is central in origin
Anti-Septin-5	Chronic cerebellar syndrome, no improvement after immunotherapy
Anti-neurochondrin	Chronic cerebellar/brainstem syndrome
Anti-Nb/AP3B2	Subacute cerebellar ataxia
Anti-Homer-3	Subacute cerebellar ataxia

SEPTIN 5 ASSOCIATED CA

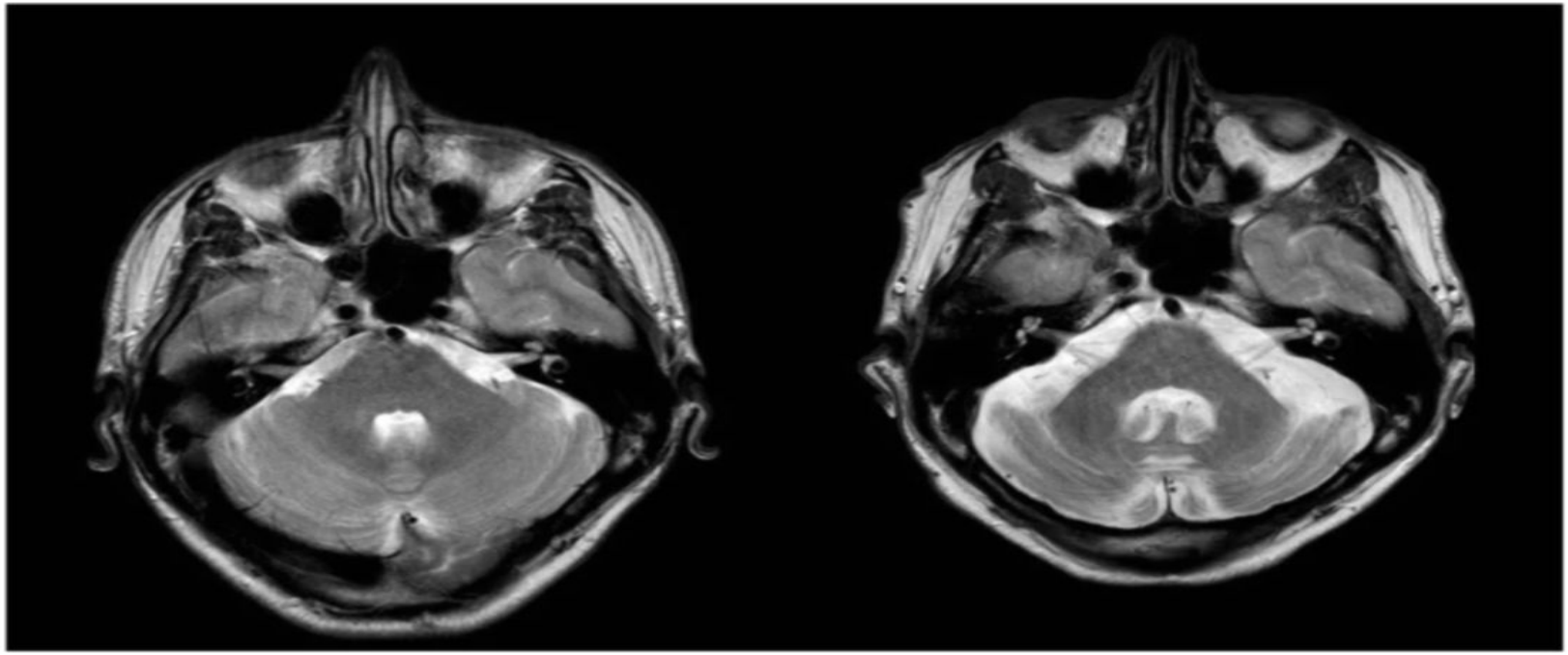


- It is a type of autoimmune cerebellar ataxia in which antibodies target septin-5, a guanosine triphosphate (GTP)-binding neural protein involved in neurotransmitter exocytosis. Septin-5 IgG is a biomarker of a rapidly progressive, but treatable, form of autoimmune cerebellar ataxia.
- Indirect immunofluorescence assay (IFA), Western blotting, immunoprecipitation, mass spectrometry, protein microarray, and cell-based transfection assays can be used to identify and confirm septin-5 as a target antigen.
- More common in elderly women. Patients have a subacute onset of cerebellar ataxia. Treatment is with immunotherapy, but if not treated the condition can be fatal.

GLUTEN ATAXIA

Male:female ratio	1:1
Mean age at onset of ataxia	53
Ocular signs	80%
Upper limb ataxia	70%
Lower limb ataxia	90%
Gait ataxia	100%
Peripheral neuropathy	60%
Enteropathy on biopsy	28%
Antigliadin antibody positive	100%
Anti-endomysium antibody positive	22%
Transglutaminase antibody positive	56%
HLA DQ2	70%
Presence of oligoclonal bands	50%

- Gluten ataxia is an immune mediated disease triggered by ingestion of gluten in genetically susceptible individuals. It could be either celiac or non-celiac gluten sensitivity. Gluten ataxias can contribute to 11.5% to 36% of all ataxias.
- The symptoms are are indistinguishable from symptoms of other forms of ataxia.
- Up to 60% of patients with gluten ataxia have evidence of cerebellar atrophy on MRI. Pathophysiology reveals patchy loss of purkinje cells throughout the cerebellar cortex. Cerebellar white matter showed astrocytic gliosis, vacuolation of the neuropil and a diffuse infiltrate mainly of T-cells.
- Treatment is gluten free diet. If symptoms don't improve immunosuppressants and immunoglobulin can be used.



MRI (patient 3) at presentation (left) and 2 years later (right) showing the rapid development of cerebellar atrophy as a result of delayed diagnosis and treatment with gluten free diet and immunosupression

Newrick, L., Hoggard, N. & Hadjivassiliou, M. Recognition and management of rapid-onset gluten ataxias: case series. *cerebellum ataxias* 8, 16 (2021). https://doi.org/10.1186/s40673-021-00139-z

ACUTE CEREBELLITIS

- Acute cerebellar ataxia (ACA) is characterized by unsteady gait and instability of the trunk, and is caused by secondary autoimmune responses to infection or vaccination. ACA is known to be the most common cause of childhood ataxia, accounting for 30% to 50% of childhood ataxia cases.
- More common in males, 2-4 years age group.
- Typical MRI findings include bilateral hemispheric cerebellar swelling with cortical and white matter T2 hyperintensities. Less commonly can present with obstructive hydrocephalus.
- Etiology - EBV, Lyme's disease, mumps, HSV1, CMV, Mycoplasma, malaria, covid-19. Post vaccination - Varicella, Hep B, rabies.
- Management involves treating the underlying infections. Diffuse cerebellar swelling should be treated with corticosteroids and mannitol. Immunoglobulins or plasmapheresis can be used. If obstructive hydrocephalus is developing surgical intervention for ventricular drainage should be done as needed. In severe cases surgical decompression of the posterior fossa can be considered. Symptoms resolve in 2-3 months.

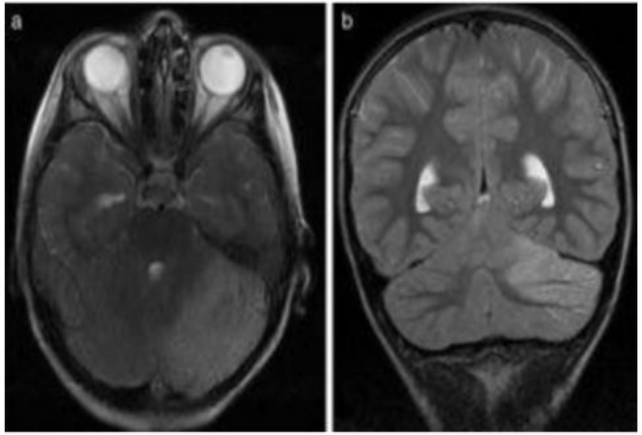


Figure 2.

(a) Axial T2-weighted brain MRI scan of patient 6. Signal hyperintensity in the left cerebellar cortex. Hemicerebellitis. (b) Coronal T2-weighted brain MRI scan of patient 6. Hyperintensities affect the left cerebellar cortex exclusively; no white matter hyperintensities are observed.

García-Iñiguez JP, López-Pisón FJ, Madurga Revilla P, et al. Acute cerebellitis in paediatric patients: Our experience. Cerebelitis aguda en Pediatría: nuestra experiencia. *Neurologia (Engl Ed)*. 2019;34(5):291-299. doi:10.1016/j.nrl.2017.01.006

PARANEOPLASTIC CEREBELLAR ATAXIA

- Paraneoplastic cerebellar ataxia also known as paraneoplastic cerebellar degeneration is one of the more commonly seen paraneoplastic neurological syndromes. It is caused by immune-mediated injury to cerebellar Purkinje cells by onco-neuronal antibodies causing acute to subacute cerebellar dysfunction.
- It is associated with multiple malignancies but, most commonly, breast and pelvic malignancies. PCA has also been reported in patients with Hodgkin lymphoma, gastric cancer, prostate cancer, and small cell lung cancer. It is very rare and is thought to affect less than 1% of patients with malignancy.
- Patients can present initially with mild symptoms such as unsteady gait, double vision, and difficulty with fine hand movements which can progress to limb and truncal ataxia. It can include brainstem causing dysphagia, dysarthria and nystagmus. The onset of cerebellar symptoms can precede the diagnosis of malignancy by months to years.
- Multiple onconeural antibodies were detected in patients with PCA and are thought to be the cause of cerebellar Purkinje cells injury. Anti-Yo antibody is the most commonly detected and is usually associated with breast and gynecological malignancies.

DIAGNOSIS AND MANAGEMENT OF PCA

To diagnose a patient with definitive PCA:

- Patient must have severe cerebellar symptoms for less than 12 weeks with a normal brain MRI
- Must also have a moderate disability with at least a score of 3 on the Modified Rankin Scale (MRS)
- Clinical evidence of both appendicular and truncal ataxia must be present
- Established diagnosis of cancer within 5 years of symptoms onset

Patients with cerebellar symptoms and detectable onconeural antibodies are also considered to have definitive PCA.

Management depends on early identification and treatment of underlying malignancy. Immunotherapy can also be used in addition to it. Patients with PCA have poor prognosis. The worst survival rates is with anti-yo and anti-hu antibodies.

Antibody	Related cancer
Anti-Yo	Breast, gynecological tumors
Anti-Hu	Small cell lung cancer
Anti-Tr[1]	Hodgkin's lymphoma
Anti-CV2[2]	Small cell lung cancer, thymoma
Anti-Ri	Breast, ovaries, small cell lung cancer, neuroblastoma
Anti-Ma2	Testicles, lung cancer
Anti-VGCC	Small cell lung cancer
Anti-SOX1	Small cell lung cancer
Anti-ZIC4	Small cell lung cancer

Pedroso JL, Vale TC, Braga-Neto P, et al. Acute cerebellar ataxia: differential diagnosis and clinical approach. *Arq Neuropsiquiatr*. 2019;77(3):184-193. doi:10.1590/0004-282X20190020

MILLER FISHER RELATED ATAXIA

- Miller Fisher syndrome (MFS) is a variant of Guillain-Barre Syndrome (GBS). The predominant features of MFS are ophthalmoplegia, areflexia, ataxia with a peripheral neuropathy being only a very mild clinical feature.
- Ataxia is often the initial presenting symptom in FS and can be quite severe, causing a gait disturbance. It affects more men than women with an approximate gender ratio of 2:1 and a mean age of 43.6 years at the onset of disease.
- Anti-GQ1b antibody is present in the serum of more than 85% of patients with FS, but it is not specific to FS. Their titers have been shown to correlate with clinical severity of the disease.
- Miller Fisher syndrome is associated with direct cerebellar involvement demonstrated by abnormal spectroscopy of the cerebellum during clinical evidence of ataxia and normalization of the spectroscopy on clinical recovery.
- MFS is mainly treated with adequate supportive care, pain control, respiratory support as needed, and immunotherapy. Severe cases are treated with immunoglobulins and plasmapheresis. The outcome of MFS is usually good with a case fatality of less than 5%. The mean recovery times range between 8 to 12 weeks.

ANTI-GAD ASSOCIATED ATAXIA

- Anti-glutamic acid decarboxylase antibody (GAD-ab) associated cerebellar ataxia is a rare, but increasingly detected, autoimmune neurological disorder characterized by the clinical presence of a cerebellar syndrome concomitant with high GAD-ab levels in serum and cerebrospinal fluid. It is seen in association with other autoimmune diseases, mainly T1DM.
- Glutamic acid decarboxylase (GAD) is a major enzyme of the nervous system that catalyzes the conversion of glutamate to γ-aminobutyric acid (GABA). It is present in the neuronal cells and pancreatic cells.
- The disease affects mostly women in their sixth decade of life with a mean clinical progression time of 6 years. Patients develop insidious or subacute onset gait ataxia, nystagmus and cerebellar dysarthria.
- Cerebrospinal fluid analysis may be normal or may show oligoclonal bands, mild pleocytosis and intrathecal synthesis of GAD antibodies. MRI can show cerebellar atrophy.
- Immunotherapy regimens such as glucocorticoid, intravenous immunoglobulin, plasma exchange, and immunosuppressive agents in varying combinations are the mainstay of the treatment. The response to treatment is variable, with complete remission being rare.

Steroid-responsive encephalopathy with autoimmune thyroiditis (SREAT)

- SREAT is also known as Hashimoto encephalopathy. The main clinical presentation is encephalopathy; however, patients may exhibit associated neurological features including seizures, movement disorders such as myoclonus or tremor, and psychosis. Cerebellar ataxia without encephalopathy is a rare presentation. Ataxia is slowly progressive like degenerative ataxia. Median age of presentation is 53.
- The most striking abnormality is raised antithyroid antibodies. Antithyroid peroxidase antibodies are markedly elevated with or without elevated antithyroglobulin antibodies. CSF analysis is normal. Brain MRI may show focal or diffuse abnormalities in 50% of patients.
- Initial treatment is with high-dose steroids titrated according to clinical response. Steroid intolerant patients may respond to cyclosporine or azathioprine. In some cases immunoglobulin and plasmapheresis can be used.

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HASHIMOTO'S ENCEPHALOPATHY: ILLUSION OR REALITY.

Khan. F., Salem, B., Thaisetthawalkul, P.; Creighton University School of Medicine, Neurology

There are few conditions in clinical neurology as elusive and protean as Hashimoto's encephalopathy. Since its first description by Brian in 1966, there have been only around 100 case reports in the literature. The clinical manifestations are myriad but mainly include either stroke like episodes and seizures or rapidly progressively dementia which can progress to coma and death if left untreated. Para clinical tests include labs, MRI, EEG and neuropsychological evaluation help in confirming the diagnosis and follow-ups.

56 years old right handed Caucasian female with past medical history of hypothyroidism developed symptoms of apathy, flattening of affect, hypersomnolence along with easy distractibility, word finding difficulty, preservation, urinary incontinence and memory disturbances for 3 weeks. Laboratory testing showed markedly elevated thyroid autoantibodies and MRI brain revealing bilateral frontal lobe while matter abnormalities involving genu of corpus callosum with cystic encephalomalacia and contrast enhancement. EEG was remarkable for bilateral frontal slowing and neuropsychological testing showing marked frontal temporal domains impairment. Additional workups did not show the other causes of cognitive impairment. Brian biopsy was declined by her family. She was treated with 1 gm of IV methylprednisone for 5 days with a tapering schedule.
All Paraclinical testing including serology, MRI, EEG, and neuropsychological evaluation showed significant improvement.

Steroid responsive encephalopathy with Hashimoto's thyroiditis (SREHT) can be diagnosed in an appropriate clinical setting with serological studies along with other Paraclinical tests. Several hypothesis including autoimmune basis, shared antigen theory, and TRH toxicity have been proposed but nothing confirmed up to date. The high index of clinical suspicion is required for the diagnosis.

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THANK YOU