Case Report

# Aceruloplasminemia with Novel Mutation, with IgG4 Related Pachymeningitis – Occam's Razor or Hickam's Dictum?

**Sai D. Yaranagula[1], Neeharika L. Mathukumalli[2], Sruthi Kola[1,2], Rukmini M. Kandadai[1,2], Vanakuru Prasad[1,2], Rajesh Alugolu[1], Rupam Borgohain[1,2]**

[1]Parkinson's Disease and Movement Disorders Research Centre (PDMDRC), Citi Neuro Centre, Hyderabad, Telangana, [2]Department of Neurology, Nizams Institute of Medical Sciences, Hyderabad, Telangana, India

## Abstract

To report a patient with concomitant aceruloplasminemia (with a novel mutation) and IgG4-related pachymeningitis and to hypothesize on the possible relation between the two diseases. Clinical, radiological, and laboratory features of a 56-year-old lady with chronic headache, bifacial palsy, and cerebellar signs are described. Pathophysiology of aceruloplasminemia leading to hyperferritinemia and consequent immune activation is elucidated. A coherent explanation of IgG4-related pachymeningitis resulting from aceruloplasminemia and hyperferritinemia is given. The patient has aceruloplasminemia with a novel nonsense mutation. She also suffers from biopsy-proven IgG4 related pachymeningitis as per standard criteria. These two seemingly unrelated illnesses are linked by hyperferritinemia. This case is a fine example of Occam's razor. Immune dysfunction and autoimmune disorders in aceruloplasminemia need to be explored through further studies to look for causal associations.

**Keywords:** Aceruloplasminemia, IgG4, novel mutation, pachymeningitis

Aceruloplasminemia is a rare autosomal recessive disorder characterized by the accumulation of iron in the brain and other areas of the body.[1] On the other hand, Immunoglobulin G4 related –pachymeningitis (IgG4R-PM) is an immune-mediated disease, characterized by inflammation of pachymeninges.[2] Here, we report a 56-year-old lady who presented with IgG4R-PM and was in addition, detected to have aceruloplasminemia with a novel mutation.

## Case Report

A 56 year old lady, presented with complaints of headaches since 2010. Headaches were intermittent, bifrontal, non-throbbing, lasting for 4-6 hours, and subsided with Non-steroidal anti-inflammatory drugs (NSAIDs). She was diagnosed to have type 2 diabetes mellitus and was on oral hypoglycemics.

In 2012, she developed sequential bifacial weaknesses, 2 months apart, for which she received short courses of steroids (oral prednisolone in tapering doses for 1 month) with mild improvement.

In 2019, she had a recurrence of headaches with new characteristics – persistent, dull aching, in the back of her head and neck with difficulty in walking. On examination, she had bifacial weakness along with facial synkinesia [Video 1], increased tone in both upper limbs along with bilateral symmetrical upper limb distal weakness (power 4/5). Sensory examination showed loss of touch and vibration in both her lower limbs. Deep tendon reflexes in both upper limbs were brisk, knee jerks were sluggish and ankle jerks were absent. Plantar reflex showed bilateral Babinski's response. Cerebellar examination showed finger nose incoordination and gait ataxia [Video 1]. Neck stiffness was present but Kernig's sign was absent.

T1 weighted MRI of the brain, post gadolinium infusion, showed diffuse pachymeningeal enhancement - along the meninges covering cerebellum, tentorium cerebelli, posterior falx, and lower brainstem with extension into cervical and dorsal spine region [Figure 1b and 1c] suggestive of pachymeningitis. However, plain MRI showed bilateral basal ganglia, red nuclei, and dentate nuclei hypointensities on T2W and SW imaging, suggestive of mineral depositions [Figure 1a]. Other investigations revealed anemia (Hb-7.4 gm%), high ESR (120 mm at 1st hour), low ceruloplasmin (8.5 mg/dl (normal 13-36 mg/dl)), low iron (35 microgram/dl (normal range 60-140 microgram/dl), high ferritin levels (1174 ng/dl (normal range 20-400 ng/dl)), and normal urinary copper levels. A nerve conduction study showed asymmetrical sensorimotor neuropathy. A liver biopsy to assess for copper

**Address for correspondence:** Dr. Rukmini M. Kandadai, Director - Parkinson's Disease and Movement Disorders Research Centre (PDMDRC), Citi Neuro Centre, Hyderabad, Telangana, India.
E-mail: rukminimridula@gmail.com

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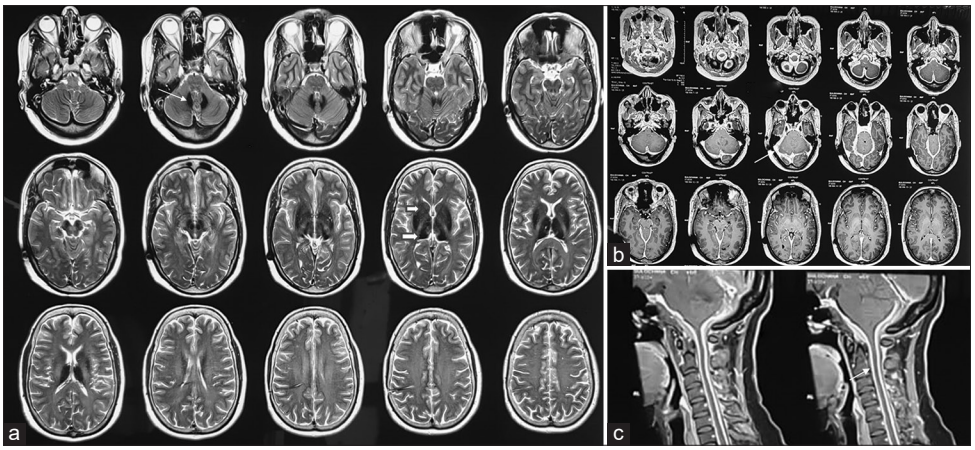


**Figure 1:** – MRI brain images. (a) - T2 weighted axial MRI brain images showing hypo intensities in bilateral dentate nuclei (thin arrow) and bilateral basal ganglia and thalami (broad arrows), suggesting extensive mineralisation. (b) - Post Gadolinium T1 weighted axial MRI brain images showing diffuse dural enhancement predominantly on tentorium cerebelli and inter hemispheric region. (c) - Post Gadolinium T1 weighted sagittal MRI Cervical spine images showing dense enhancement of meninges covering spine

levels to rule out Wilson's disease was normal. CSF analysis showed lymphocytic pleocytosis, high protein levels, and normal sugar. CECT chest showed small paratracheal lymph nodes. Serum ACE levels were normal.

To establish a definitive histopathological diagnosis for the cause of meningitis, a cervical dural biopsy was done. It showed lymphocytic infiltrate and fibrosis. Immunohistochemistry showed CD138 positive plasma cells with IgG4 positive cells >10/HPF. Based on this, a diagnosis of IgG4-related pachymeningitis was made.[2] She was treated with a pulse of Intravenous Methyl Prednisolone infusion (1 gm × 5 days) followed by Rituximab with a dose of 1 gm 15 days apart to be given every 6 months.

Whole exome sequencing was done in view of an MRI Brain showing evidence of mineralization. Genetic testing identified a novel homozygous c318 T > G (p.Tyr106Ter) mutation in exon 2 of the CP gene (chr 3:g. 148930314A > C; Depth: 46x) and was validated using Sanger sequencing. This results in a stop codon and premature truncation of the protein and is likely to be pathogenic. The patient was counseled regarding the use of deferiprone for aceruloplasminemia which the patient deferred.

## Discussion

IgG4R-PM is characterized by immune-mediated neuroinflammation of pachymeninges.[2] Clinically it can present with headaches and cranial nerve palsies, both of which were prominent in our patient.[3] Radiologically, she had diffuse pachymeningeal enhancement along the posterior falx, tentorium cerebelli, and spinal cord, encompassing cerebellar lobes and spinal cord up to D2 level. The final diagnosis of IgG4R-PM was established by biopsy as per consensus criteria published by EULAR in 2019.[2] The use of steroids and rituximab resulted in good resolution of these symptoms. Cerebellar ataxia also improved with treatment. This raises the possibility that pachymeningitis was contributing to the ataxia.

On the other hand, aceruloplasminemia is a rare autosomal recessive disease with a mutation in the ceruloplasmin gene leading to the absence of or strong reduction in the activity of ceruloplasmin.[1] Our patient had cerebellar ataxia, microcytic anemia, diabetes mellitus along with low ceruloplasmin levels, and hyperferritinemia, all of which are reported with aceruloplasminemia.[1]

MRI Brain showed features of aceruloplasminemia on the plain scan and pachymeningitis on the contrast scan. We would like to emphasize that the predominant clinical presentation to the Neurology department was for pachymeningitis. Glaring and distinctive features on contrast scans should not distract the clinician from the other subtle clinical and radiological signs. Whole exome sequencing revealed a homozygous mutation in exon 2 of the ceruloplasmin gene (c318 T > G (p.Tyr106Ter)) which leads to a stop codon and truncation of the protein. This is a novel mutation leading to aceruloplasminemia.

This patient had an unusual combination of a rare underlying genetic disease -aceruloplasminemia with a novel mutation and a relatively rare immune-mediated disorder -IgG4R-PM. Although this could have occurred by chance, increased ferritin may have triggered an abnormal immune response. This brings us to the question of Occam's razor which teaches us to associate seemingly unrelated signs versus Hickam's dictum which proclaims that a single person can have different unrelated diseases independently.[4]

Ceruloplasmin is a ferroxidase that converts Fe2 + to Fe3+, helping iron to move out of the cells and bind to transferrin. Deficiency causes the accumulation of iron in cells of various organs including the brain. There is a paradoxical increase in ferritin levels with an overall increase in iron stores, probably due to increased absorption.[1] Depending on the context, receptors, and subcellular pathways activated, ferritin is known

to have both pro-inflammatory and anti-inflammatory effects. Also, hyperferritinemia is noted in a proportion of patients with autoimmune disorders like Systemic lupus erythematosus, Rheumatoid arthritis, and Multiple sclerosis. This has led to the suggestion of a possible pathogenic role for ferritin in autoimmune diseases.[5] On similar lines, we hypothesize that the primary pathology in our patient is the genetic mutation causing aceruloplasminemia leading to high ferritin. This in turn might have triggered an inflammatory cascade leading to IgG4R-PM. We therefore propose it as an example of Occam's razor. Further observations from both clinicians and basic scientists are required to definitely establish a causal association.

## Conclusion

We hereby report a rare case of biopsy-proven IGG4-related disease and aceruloplasminemia due to a novel mutation. The occurrence of these two etiologies in one individual is very rare and may suggest an association.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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We here in report the first case of aceruloplasminemia (with novel mutation) and IgG4 related pachymeningitis in the same patient. We present a plausible hypothesis connecting the two diseases for the first time ever.

Aceruloplasminemia is a rare genetically determined illness with low ceruloplasmin and high ferritin. IgG4 related pachymeninigitis is an acquired immune mediated disease with headache and cranial nerve palsies.