Case Report

Rare Case of Lipoid Proteinosis with Bilateral Symmetrical Mesial Temporal Lobe Calcifications

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A B S T R A C T

Introduction: Lipoid proteinosis is a rare multisystem autosomal recessive genetic disorder characterized by intracellular deposition of amorphous hyaline material in various tissues like skin, blood vessels, brain, vocal cord, pharynx and esophagus. Disease is caused by mutation of extracellular matrix protein 1 gene (ECM 1). Characteristic findings are symmetrical calcifications in bilateral hippocampus, parahippocampal region and Amygdala. Pathognomonic finding is a dermatological condition, moniliform blepahoris, seen in 50 % of patients. Patients typically present with seizure disorder, depression and anxiety when CNS is involved and hoarseness of voice. We describe characteristic radiological findings in a genetically proven case.

Case Report: A 24 year old boy with complaints of seizure, depression, hoarseness of voice and skin problems presented to neurology clinic. Patient was initially evaluated with detailed family history and EEG was done which was normal. Patient was referred for MRI study of brain. Characteristic bilateral symmetrical T1 and T2 hypointense foci of calcification was seen in bilateral hippocampus and amygdala. CT scan brain was done for correlation which confirmed MRI findings. On basis of clinico-radiological correlation, diagnosis of Lipoid Proteinosis was made.

Conclusion: We highlight this case report for being rare and undiagnosed. This identity should be considered as a differential diagnosis for patients presenting with seizure disorder and skin problems and typical radiological findings. Clinico-radiological approach is required for establishing a diagnosis.

Keywords: Lipoid Proteinosis, Symmetrical Amygdala Calcification, Mesial Temporal Lobe Calcification, ECM 1 Gene.

INTRODUCTION

Lipoid proteinosis or Urbach-Wiethe disease is a rare genodermatosis characterized by multisystem involvement and intracellular deposition of amorphous hyaline material in various tissues like skin, blood vessels, brain, vocal cord, pharynx and esophagus.[1,2] There is mutation of the extracellular matrix protein 1 gene (ECM 1 gene).[3]

Patients typically present with skin manifestation first and later develop hoarseness of voice. Many develop neurological symptoms like seizure, depression and anxiety.

We described a case of 24 yr old young boy who presented with similar complains and characteristic radiological findings in genetically proven case.

CASE REPORT

A case of 24 yr old young adult, born out of consanguineous marriage presented to a neurology clinic with complains of seizures episodes with straightening of upper and lower limbs and post-ictal headache and lethargy. Patient had skin problems and beaded papules on eyelids (Fig. 1, 2) since few years. Patient also had history of depression and hoarseness of voice. Physical examination showed macroglossia. Initial evaluation showed normal EEG. He was referred to radiology centre for MRI.

MR imaging of the brain showed bilateral symmetrical T1 and T2 hypointense foci (Fig. 3, 4) with blooming on susceptibility weighted images (Fig. 5) in bilateral amygdala and hippocampal region. On CT correlation (Fig. 6) the involved region showed dense calcifications in

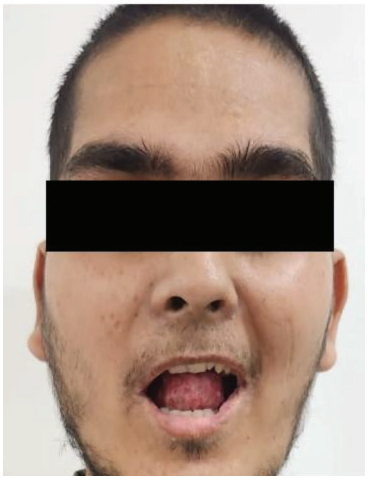

Figure-1: Photograph showing affected patient with skin problems.

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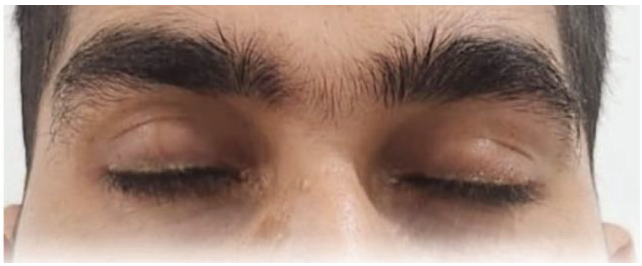

Figure-2: Photograph showing affected patient with beaded papules along the eyelids.

both hippocampal head and amygdala. Rest of the brain parenchyma was unremarkable.

Family tree evaluation showed total of 6 siblings with patient being the fourth child. Similar complaints were also seen in second (Fig. 7) and sixth child. Routine blood examination did not reveal any specific etiology. Plasma glucose (Random) was 106 mg/dl and serum calcium was 9.3 mg/dl.

Based on clinic-radiological approach, diagnosis of lipoid proteinosis / Urbach-Wiethe disease was made. Other close differentials were ruled out. Possibility of calcified glioma

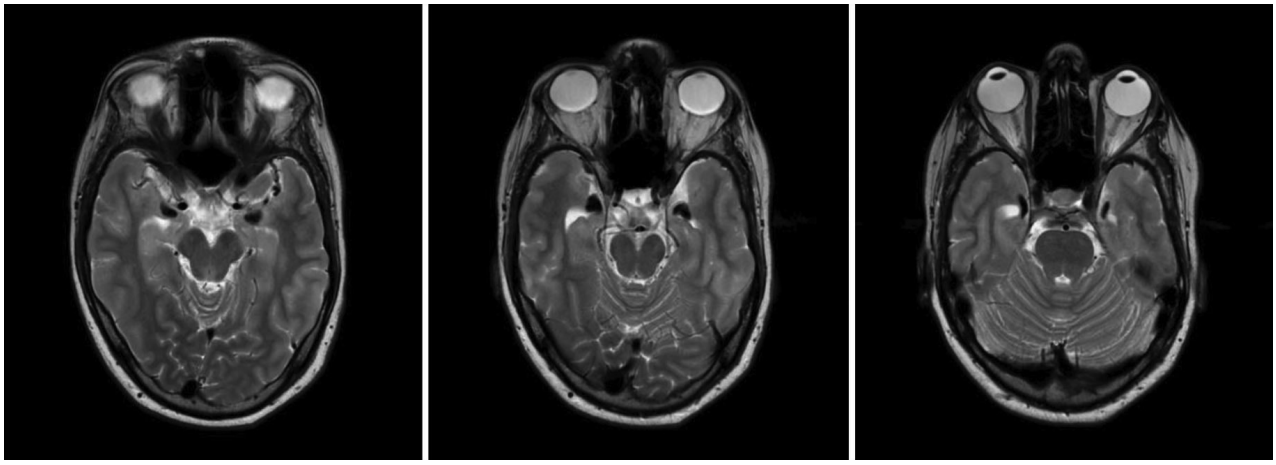

Figure-3: T2 Wt. axial images showing symmetrical hypointensities / calcification in bilateral amygdala and hippocampal region.

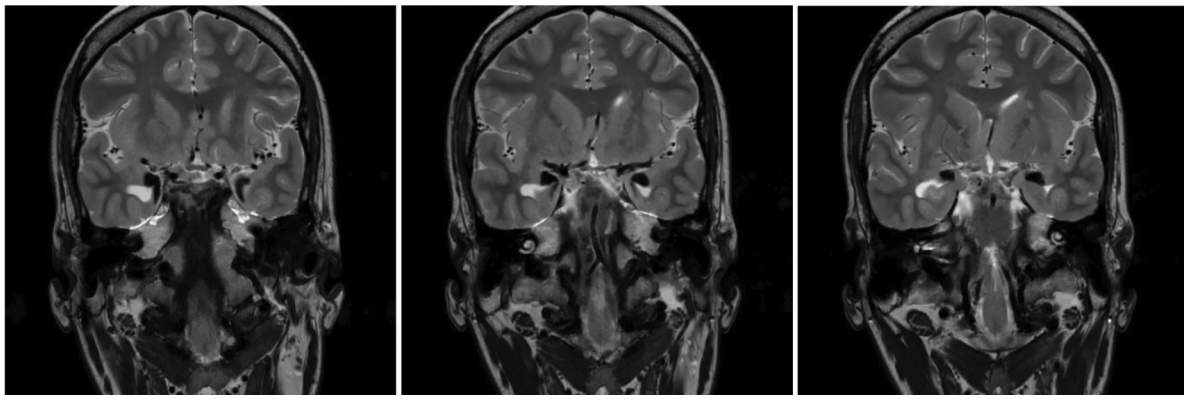

Figure-4: T2 Wt. coronal images showing symmetrical comma shaped or curvilinear hypointensities / calcification in bilateral amygdala and hippocampal region.

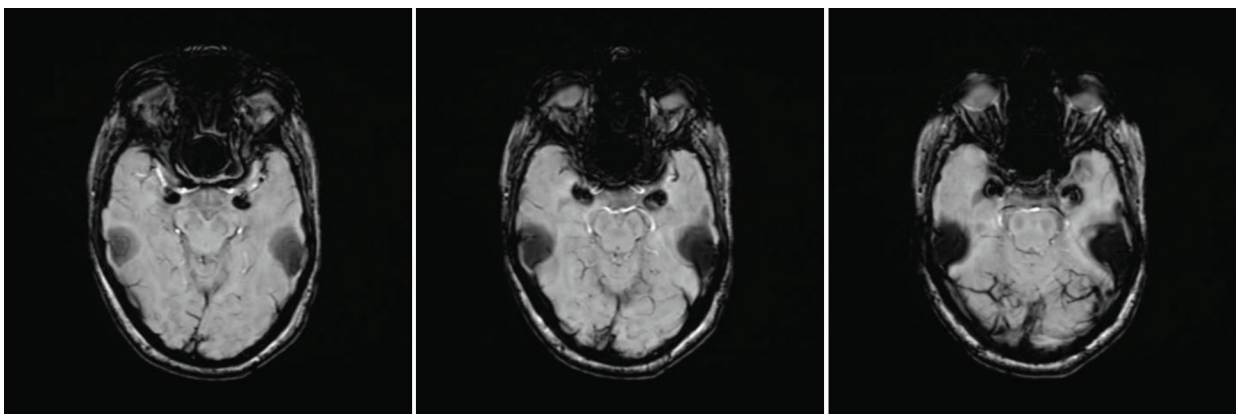

Figure-5: Susceptibility weighted images showing blooming due to mineralization in bilateral amygdala and hippocampal region.

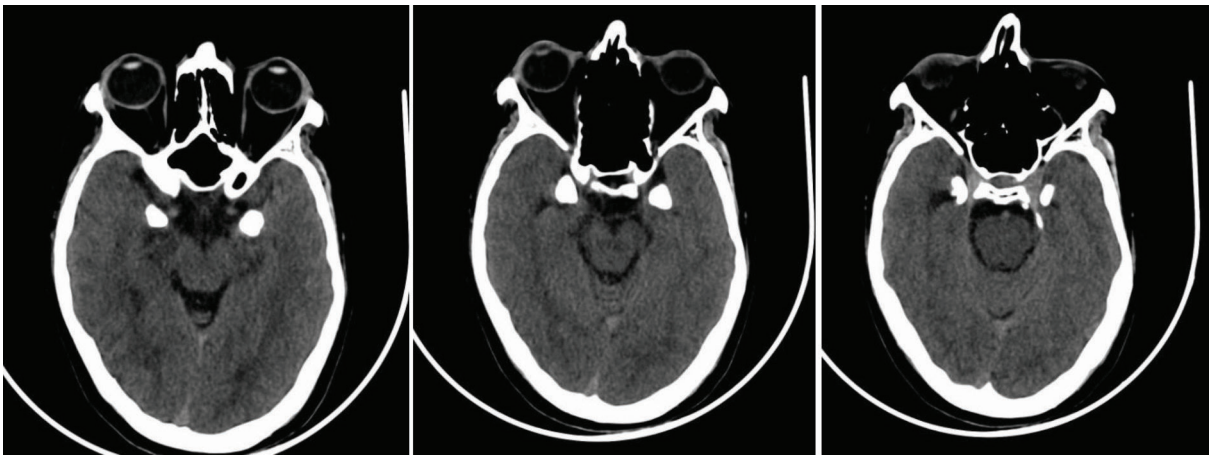

Figure-6: CT images showing dense calcifications in bilateral mesial temporal lobes and amygdala.

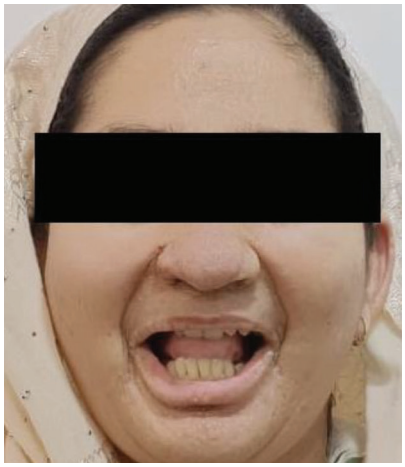

Figure-7: Photograph showing affected patient elder sibling (sister) with similar skin problems and premature aging.

was ruled out by bilateral symmetrical involvement. Healed herpes encephalitis was ruled out as it shows dystrophic temporal lobe calcification.

Patient was advised for genetic study (whole exome sequencing) which detected likely pathogenic variant in exon 1 of the ECM1 gene (ECM1 variation). (Fig. 8)

DISCUSSION

Lipoid proteinosis is also known as Urbach Wiethe disease or Hyalinosis cutis et mucosae.[4] It is a rare, multisystem disease, autosomal recessive genodermatosis characterized by mutation in the ECM 1 gene on chromosome 1q21. ECM1 gene mutation leads to deposition of hyaline material in dermis, mucous basement membrane and blood vessels. Less than 500 cases have been reported worldwide with even lesser cases identified in Indian population.

RESULTS

LIKELY PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

SNV(s)/INDELS

Gene# (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification$
ECM1 **(+)** (ENST00000369047.9)	Exon 1	c.39T>G **(p.Tyr13Ter)**	Homozygous	Urbach-Wiethe disease (OMIM#247100)	Autosomal recessive	Likely Pathogenic **(PVS1, PM2)**

Copy Number Variants CNV(s)

No significant CNVs for the given clinical indications that warrants to be reported was detected.

VARIANT INTERPRETATION AND CLINICAL CORRELATION

Variant description: A homozygous nonsense variant in exon 1 of the ***ECM1*** gene **(chr1:g.150508248T>G; Depth: 148x)** that results in a stop codon and premature truncation of the protein at codon 13 **(p.Tyr13Ter; ENST00000369047.9)** was detected (Table). This variant has not been reported in the 1000 genomes, gnomAD (v3.1), gnomdAD (v2.1), topmed and our internal databases. The *in silico* prediction# of the variant is damaging by MutationTaster2. The reference codon is conserved across species.

Figure-8: Whole exome sequencing detected likely pathogenic variant in exon 1 of ECM1 gene (ECM1 variation).

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Patients present with abnormal scarring and premature aging of skin.[3,5] Hoarseness of voice is seen in around two third of the patients due to deposition of hyaline material within the larynx which progresses with time.[6]

Moniliform blepharosis is a pathognomic dermatological presentation commonly seen in nearly half of the patients.

CNS involvement is seen in two third of the patients with infiltration into the capillaries of the hippocampus and amygdala which later progresses to calcium deposition in the perivascular space.[7] On microscopy, it appears as amorphous calcification surrounded by gliotic tissue and calcified thickened capillary walls.[2] Amygdala is a part of the limbic system that plays an important role in emotion, modulation of attention, learning and emotional long term memory.[8,9] Amygdala involvement is pathognomic and becomes prominent with longer duration of the disease. Neurological presentation commonly are seizure disorder, migraine, depression and anxiety disorder.

Typical radiological findings include dense bilateral mesial temporal lobe calcifications.

On CT images, these look like curvilinear or comma shaped calcification in amygdala, hippocampus, parahippocampal gyrus and striatum.

On MR images, these calcific areas appear hypointense on T1 and T2 weighted images showing blooming on T2* GRE images or susceptibility weighted images.

Differential diagnosis of medial temporal lobe calcifications include:

- Calcified glioma - but these generally are never symmetrical or bilateral.
- Healed herpes encephalitis commonly show temporal lobe dystrophic calcifications as a later sequelae to herpes encephalitis.[10]

CONCLUSION

Brain calcifications mainly in striatal region and deep nuclei can occur in many metabolic and inherited conditions. However selective brain calcifications in specific sites such as amygdala, hippocampal region and corpus striatum along with neurological and cutaneous manifestation are pathognomic for lipoid proteinosis under proper clinical scenario.

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