

## LIPOID PROTEINOSIS

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**L**ipoid proteinosis (LP) is a rare entity with an insidious onset and a gradually progressive clinical course. It variably affects the entire body and predominantly manifests through lesions of skin, mucous membrane and brain.

The name Lipoid Proteinosis is a misnomer as no abnormality has been demonstrated in lipid metabolism till date. The name is based on the fact that on histology the material deposited in the tissues resembles lipids and proteins. Although most cases have been seen in the Caucasian races in South Africa and Central Europe, few cases have also been described from Asia.<sup>12,6</sup> Till date not more than 500 cases have been reported worldwide. Hence the actual data about incidence and prevalence is not built up.

No definitive age, sex or race predilections exist. There is documented autosomal recessive inheritance as there is usually history of consanguinity among unaffected parents.<sup>21</sup> Autosomal dominant inheritance due to mutant genes has also been documented and only this subtype of parent disorder is associated with mental sub normality.<sup>12</sup>

In the gene encoding extracellular matrix protein 1 (*ECM1*) on band 1q21 there occur loss of function

Lipoid Proteinosis (LP) has a chronic course and a potential to affect quality of life adversely. It usually comes with a genetic tag and requires a multidisciplinary approach for managing the patient as well as their descendents.

**Key words:** lipoid proteinosis, intracranial calcification, skin lesions.

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mutations. Patients with exon 7 mutations display slightly milder clinical features, while mutations in exon 6 result in a more severe phenotype.<sup>7,8</sup>

Normally the *ECM1* gene produces a glycoprotein which is expressed in skin, mucosa and the entire human viscera. Mutation in this gene leads to deposition of hyaline like material in the skin and viscera in abnormal amounts which is the cause of clinical manifestations. These deposits stain positive with Periodic Acid-Schiff stain, are diastase resistant and negative for Congo red.<sup>20</sup>

### Historical Background

In 1908, Seibman presented the initial report on LP.<sup>12</sup> In 1929, it was described in detail and named as "Lipoidosis cutis et mucosae" by Urbach and Weithe.<sup>24</sup> Moynahan suggested disturbed mucopolysaccharide metabolism as the probable cause in 1966.<sup>16</sup> Later in 1967 Rosenthal and Duke proposed quasidominant pedigree pattern resulting from consanguinity.<sup>19</sup> Gordon et al. documented the recessive mode of inheritance in 1969.<sup>5</sup> Newton et al. (1971) reported neuropsychiatric symptoms and considered intracranial calcifications as pathognomonic.<sup>17</sup> Meenan et



Figure 1. Hyperkeratosis in right elbow



Figure 3. Depigmented lower lip and almost tied tongue due to deposition of hyaline like material in frenulum

al. in 1978 found that bilateral intracranial calcifications are present in at least 70% of cases.<sup>14</sup> Bauer et al. (1981) presented evidence that this is in fact a lysosomal storage disease with variable manifestations.<sup>3</sup> Leonard et al.<sup>13</sup> first reported brain CT findings of LP. In 1985, Emsley and Paster reported that these patients have memory impairment, paranoia, and bilateral temporal lobe calcification.<sup>4</sup> Stine and Smith (1990), suggested that this may be a pleiotropic gene that is dominant in selection and recessive in clinical manifestation.<sup>22</sup> Adolphs et al. demonstrated complete bilateral destruction of amygdala and sparing of hippocampus and all neocortical structures in 1994.<sup>1</sup> Hamada et al. mapped LP to chromosome 1q21 at D1S498 in 2002<sup>7</sup> and in 2003, concluded that mutations outside exon 7 exhibit more severe mucocutaneous lipoid proteinosis phenotype.<sup>8</sup>

Thornton et al. (2008) extensively assessed thirty-four adults living with LP (>10% of the world population) with standardized neuropsychiatric and neuropsychological measures and concluded that medial temporal areas are involved in cognitive and emotive processing.

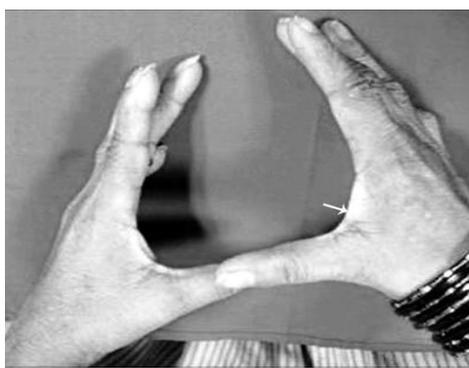


Figure 2. Wax like appearance of hands

### Pathology

Histologically, LP is characterized by deposition of hyaline like material at the level of the basement membrane (resulting in its thickening at the dermoepidermal junction), papillary dermis, surrounding blood vessels, and around

adnexal epithelia especially sweat coils.<sup>23,9</sup> Ultra structural examination reveals concentric rings of excess basement membrane surrounding blood vessels, and irregular reduplication of lamina densa at dermoepidermal junction resulting in onion-skin appearance.<sup>15,9</sup>

Biochemically, this material is characterized by decrease in type-1 collagen with overproduction of type-4 or basement-membrane collagen. The hyaline deposits in the biopsies examined consist of a carbohydrate-protein complex containing hyaluronic acid and probably chondroitin-sulphate, plus large amounts of lipids.<sup>15,9</sup>

### Clinical Features

Patients present with persistent rough and feeble hoarse cry which can begin right from infancy is the hallmark. Skin initially shows self limiting vesicular eruptions which heal with scarring. Diffuse thickening and wax like appearance predominates the next phase. Moniliform blepharosis or beaded eyelid margin is also seen in this phase. Tough skin plaques gradually appear on extensor surfaces (Figure 1). Wax like appearance of hands (Figure 3) and depigmented lips (Figure 3) are also seen. On histopathology there is deposition of hyaline like material at dermo-epidermal junction (Figure 4).

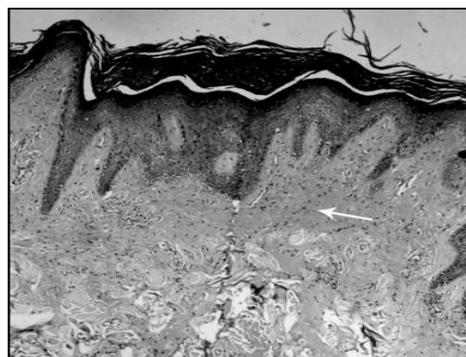


Figure 4. Photomicrograph (10x) shows hyalinelike deposits at dermo-epidermal junction (H & E stain)



Figure 5. Lateral radiograph of skull shows open C shaped suprasellar calcification

Scalp shows areas of variable hair loss. Lips and tongue become thick, heavy and exhibit gradual reduction in mobility. Laryngeal and airway involvement manifests as hoarse voice, dyspnoea and even dysphagia. Deposits of hyaline like material can be seen as filling defects in upper aero-digestive tract.

Radiological hallmark is the presence of bean to comma shaped intracranial calcifications in the temporal lobes in amygdala which is more evident in patients with longer disease duration. Epilepsy, when present, may be related to these calcifications. Patients with LP should be followed with MRI/CT in order to identify these abnormalities.<sup>22</sup>

Proper plain radiographs (Figure 5) and CT (Figure 6) are adequate for a definitive diagnosis, while MRI (Figure 7 & 8) is useful to assess the brain in totality.

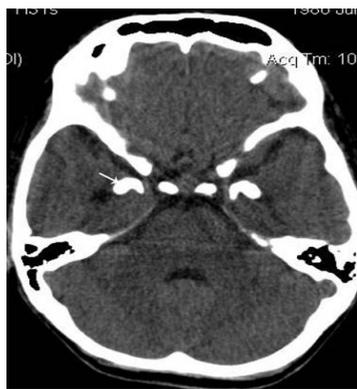


Figure 6. Plain CT brain shows bilateral comma shaped calcifications in amygdala

Henkelman et al<sup>24</sup> studied high signal intensity in MRI images of calcified brain tissue and proposed that particulate calcium can reduce T1 relaxation times by surface relaxation mechanisms. As calcium concentration progressively increases, there is first an increase in signal intensity (due mostly to T1 shortening) followed by a decrease in signal intensity. Thus for concentration of calcium particulate for upto 30% by weight, the signal intensity on standard T1-weighted images increases but

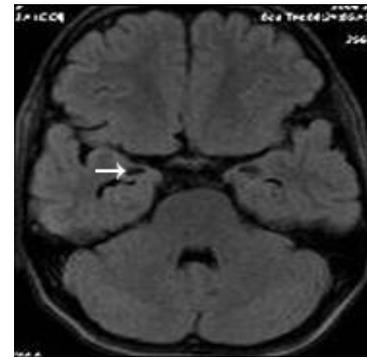


Figure 7. Axial T1W MRI brain shows bilateral comma shaped calcifications in amygdala

subsequently decreases. No other reference could be found to prove or disapprove this proposition.

There is a possibility of social stigma due to external appearances and inability to talk or eat properly due to restricted tongue movements. Subjects with LP have a high incidence of neuropsychiatric disorders and perform poorly on facial recognition of positive and negative emotions and on many neuropsychological measures. These findings are consistent with involvement of the parahippocampal medial temporal areas in cognitive and emotive processing.<sup>15</sup>

The amygdalae perform a primary role in the processing and memory of emotional reactions and support a variety of functions including behavior, long term memory and olfaction.

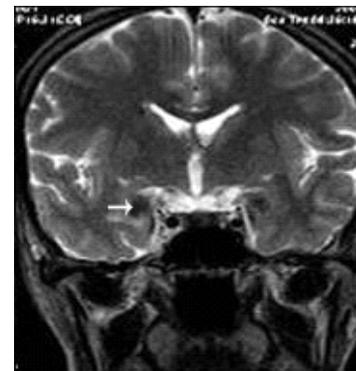


Figure 8. Coronal T2W MRI shows hypo intense calcifications in amygdala

Destruction of the amygdala (para hippocampus), while sparing the hippocampus and all neocortical structures and intracranial calcification leads not only to seizures but also impaired social and emotional behavior. Memory defects due to inability in recognizing facial emotions coupled with bouts of rage which occur as the patient cannot read the expression of fear on other persons face.<sup>12</sup> Erythropoietic protoporphyria (EPP) needs to be differentiated from LP, in which unlike LP the deposition of PAS-positive material is less dense around blood vessels and never around sweat glands. Increased protoporphyrin levels in erythrocytes

are also seen in EPP.<sup>22, 18</sup> Deposits in amyloidosis and xanthomas chemically differ from those in LP.

No permanent cure is available for LP till date. Only symptomatic medical treatment is being used. For skin lesions treatment trials worldwide include dimethyl sulphoxide, tretinoin, intralesional heparin and D-penicillamine. However none of these medicines have shown consistent good results in one and all. When skin lesions fail to respond to medical therapy, dermabrasion for skin lesions is done.

Carbon Dioxide laser for lesions of eyelids and aerodigestive tract is also under consideration. When the patient has seizures, anticonvulsants are used for medical management. Essentially the treatment of LP involves a multidisciplinary approach of a team consisting of a dermatologist, pediatrician, physician, neurologist, ENT surgeon, psychiatrist and even medical geneticist.

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