Lipoid proteinosis (Urbach-Wiethe syndrome)

V. FEILER-OFRY,¹ A. LEWY,³ L. REGENBOGEN,² D. HANAU,³
M. BAT-MIRIAM KATZNELSON,⁴ AND V. GODEL¹

From the ¹Medical Corps I D F, the ²Goldschleger Eye Institute, the ³Department of Dermatology, and the ⁴Department of Human Genetics, Sheba Medical Center, Tel Hashomer, Tel Aviv University School of Medicine, Israel

SUMMARY A Jewish-Iranian family suffered from lipoid proteinosis. The 8 affected siblings were from consanguineous matings and presented a wide range of phenotypic expressions. Minimal manifestations in 2 heterozygote carriers and the possibility of autosomal recessive inheritance are discussed.

Lipoid proteinosis or Urbach-Wiethe's disease (Urbach and Wiethe, 1929) is a rare hereditary disorder due to a disturbance in the metabolism of lipids and proteins involving the skin and mucous membranes. It starts in early childhood and is characterised by a deposition of plaques on the mucous membranes, an eruption on the face and extensor surfaces of the skin, and nodular formations on the margin of the eyelids (Blodi *et al.*, 1960). The distribution of the lesions, their chronic nature, and their histological picture seem to be pathognomonic.

We here present a family of several individuals with the characteristic features of lipoid proteinosis and analyse the frequency and range of clinical

anomalies in order to document the definitive phenotypic spectrum of this condition.

Family study

Fig. 1 presents the pedigree of a Jewish-Iranian family. The proband's maternal grandfather (I 2), who was told that he was normal, had 2 children from his first marriage (II 4 and II 5) and 1 child from his second marriage (II 1). The first 2 children married their first cousins (II 3 and II 6) and gave birth to 7 children in each family, with a high rate of affected individuals (III 2, III 4, III 5, III 8, III 10, III 15). The only child from his second marriage (II 1) became the grandfather of 2 other affected nephews (IV 1 and IV 2).

From the 17 examined cases 8 were found to be phenotypically fully affected, while 2 others were

Fig. 1 Family pedigree

Table 1 Summary of anomalies

Case no.	Age	Sex	Ocular findings		Dermatological findings	Laryngoscopic findings		Buccal findings	
			Monoliform blepharosis	Solitary nodule		With hoarseness	Without hoarseness	Patchy infiltration	Dental abnormalities
1	19	Male	+	-	+	+	-	+	+
2	32	Female	+	-	+	+	-	+	+
3	50	Female	-	-	-	-	-	-	+
4	3	Male	-	+	-	+	-	+	-
5	11	Male	+	-	+	+	-	+	+
6	13	Male	+	-	+	+	-	+	+
7	21	Male	+	-	+	+	-	+	+
8	48	Male	-	-	-	-	+	-	-
9	15	Male	-	-	-	+	-	+	-
10	9	Female	+	-	+	+	-	+	-

Fig. 2 Yellowish pearly nodules along the free margin of the eyelid

considered partially affected. A summary of the anomalies in these 10 cases are tabulated in Table 1 and they are reported below.

CASE 1 (III 10)

The propositus, a 19-year-old man, was referred for an eye examination because of headache. He gave a history of non-progressive hoarseness since early childhood. On ocular examination numerous small yellowish pearly nodules were found along the free margin of both eyelids at and among the roots of the eyelashes (Fig. 2). The lashes grew normally through them, and no trichiasis or loss of cilia was noted. Posteriorly to the nodules, where the change from skin to conjunctiva occurred, a thickened hyalinised line was found. Laryngoscopy revealed a polyp-like irregularity on one of the vocal cords. The posterior wall of the pharynx showed

many yellowish patches. The frenulum was indurated, with reduced mobility of the tongue. The entire buccal mucosa was pale, and multiple white-yellowish patches were seen on the inner surface of the lower lip (Fig. 3). The premolar milk teeth of the lower jaw were missing. Multiple varioliform scarrings were found on the skin of the face, on the forehead, cheeks, and chin. The same findings were disclosed on the elbows and knees, together with localised areas of hyperpigmentation. All these scars appeared after a vesicular eruption at the age of 2 years.

CASE 2 (III 15)

A 32-year-old woman, the sister of the propositus, had similar lesions on the ocular, oral, and cutaneous areas. The small nodules situated on the margins of all 4 lids were translucent and waxy. Her face had

Fig. 3 White-yellowish patches on the inner surface of the lower lip

the characteristic pox-marked appearance. Her voice was hoarse owing to the infiltration of the posterior pharynx and buccal mucosa with irregular yellowish plaques. She was the mother of 3 normal girls.

CASE 3 (II 5)

A 50-year-old woman, the mother of the above 2 cases, had no lesions. However, at the age of 30 she lost all her teeth in a short period of time. She knew of no affected relatives in either generation I or II.

CASE 4 (III 2)

A 3-year-old boy was known to have hoarseness from early infancy. Areas of induration of the buccal mucosa and the back of the tongue were found. Along the free margin of each eyelid a solitary pearly nodule was detected. There was no skin involvement at this age. Only after 6 months, when seen again, an impetiginous eruption occurred on the skin of his face and shoulders, leaving, after healing, small punched-out scars. At this time there were already 3 to 4 discrete nodules on the upper lids.

CASE 5 (III 4)

An 11-year-old boy presented the typical picture of the disorder. The clinical manifestations included hoarseness and widely distributed skin changes. In addition to the former cases there was induration of the lips with fissuring of the commissurae. The dentition was abnormal, since the premolar and molar milk teeth of the lower jaw had not erupted.

CASE 6 (III 5)

A 13-year-old girl developed normally until the age of 10 months, when an erythematous, pruritic eruption appeared on her face, elbows, and knees. The eruption healed, leaving pigmented varioliform scars and marked hyperkeratosis on the skin of the elbows and knees. As a young child her voice was hoarse, but it improved in the course of years. The clinical picture was similar to that found in the propositus except for normal laryngoscopic findings. The premolar and molar milk teeth of the lower jaw did erupt, but the teeth remained smaller than usual.

CASE 7 (III 8)

A 21-year-old man presented the full clinical picture of the disease. Multiple discrete and confluent yellowish nodules were among the lashes of both eyelids, and pigmented punched-out scars of different sizes covered his face. He had a roughened skin over his elbows and knees. The tongue was thickened, with loss of papillae, the vocal cords were

irregularly indurated, and numerous whitish patches were seen on the buccal mucosa as far as the larynx.

CASE 8 (II 4)

A 48-year-old man, the father of the last 4 cases, had no complaints and appeared normal clinically. Laryngoscopy, however, revealed 2 white small nodules at the posterior third of the vocal cords.

CASE 9 (IV 2)

A 2-year-old boy had a high-pitched hoarse cry when examined. At laryngoscopy a diffuse infiltration of the vocal cords and the buccal mucosa was seen. Neither skin nor eye involvement has yet been found.

CASE 10 (IV 2)

A 9-year-old girl gave a history of hoarseness since the age of 2 years. About the same time she had impetiginous eruptions on her face and elbows. On examination numerous pale yellow-brown scars were seen on her forehead, cheeks, and chin. At the free margin of the superior eyelids 3 to 4 pearly nodules were found (Fig. 4). On the buccal mucosa were scattered small areas of induration. The tongue had reduced mobility.

It is interesting to note that the affected individuals in these families resemble each other more than their own unaffected relatives.

In all the above reported cases biopsy was taken from the skin, buccal mucosa, and palpebral nodules. Histological examination revealed a papillomatous epidermis with a thickened dermis due to hyaline material arranged in homogeneous bundles. The hyaline material stained pale pink with haematoxylin and eosin. In the hyaline areas the nuclei of the fibroblasts and the vascular endothelium were well preserved. A homogeneous eosinophilic hyaline

Fig. 4 A few pearly nodules along the upper eyelid

Fig. 5 The histological changes in the upper dermis. Numerous vessels surrounded by a hyaline mantle (arrows) (Haematoxylin-eosin)

mantle surrounded the vessels and sweat glands (Fig. 5). A positive reaction to Sudan III staining showed the presence of neutral fats.

Laboratory investigations were carried out in all cases. Values for cholesterol, triglycerides, total lipids, lipoproteins, total proteins, and serum glucose were within normal limits. X-ray of the skull and an electroencephalograph showed no abnormalities.

Discussion

The clinical abnormalities in our patients leave no doubt that they are suffering from lipoid proteinosis. Though the expression and degree of organ involvement vary, the total pattern of anomalies is specific enough to support such a diagnosis.

The ocular findings did not cause any symptoms and can be considered almost pathognomonic. Their first appearance was as a solitary pearly nodule at the free margin of the eyelid (case III 2) or as 3 to 4 nodules at the root of the eyelashes (case IV 2). In neither case had the band of hyalinisation at the conjunctival site of the ciliary margin yet appeared. Only in more advanced stages (Cases III 10, III 15, III 4, III 5, III 8) did the papules appear in rows along the margin of the eyelids with the characteristic picture of moniliform blepharosis. Neither conjunctival nor corneal deposits were noted. There was no loss of lashes or trichiasis in any of our cases.

The dermatological picture in lipoid proteinosis is variable, but in our cases 2 clinical findings predominated—multiple varioliform scarrings on the skin of the face, elbows, and knees, and hyperpigmentation in the same areas. These cutaneous

changes appeared as a result of vesicular eruptions with long-standing secondary infection in early childhood, followed by pitted scars which became pigmented. The skin lesions were identical in all cases, but their intensities differed in accordance with the age of the patient. The older the patient the more prominent were the lesions.

One of the earliest and commonest clinical symptoms was hoarseness, probably due to the involvement of the mucous membranes of the oral pharynx and incomplete closure of the thickened vocal cords. The oral tissues were infiltrated with yellowish-white patches with the characteristic thickening and limited mobility of the tongue. The faulty dentition found in many of the affected individuals could be explained by the hyalinisation and progressive obstruction of the orifices of Stenson's ducts.

Lipoid proteinosis is a systemic disorder. Besides the skin and mucous membranes it may involve many other viscera (Caplan, 1967) and even the central nervous system (Hewson, 1963). Although the exact aetiology of the disease is unknown, several theories have been put forward to explain its possible mode of origin and pathogenesis. Suggestions that the deposits were protein-bound phospholipids (Urbach and Wiethe, 1929) were followed by theories that the primary defect was a degeneration of elastic and collagen fibres, with release of carbohydrates followed by a secondary deposition of lipid material (Katznelbogen and Ungar, 1957). Electron microscopic studies (Jensen *et al.*, 1972) pointed to a vascular leakage in the pathogenesis of the disease. The histological picture in our cases shares some features with histiocytosis X, but this pathological similarity does not prove an aetiological identity, and the consistency of the reported cases suggests that they do not represent the same entity.

The pedigree indicates an autosomal recessive inheritance to be the most likely in these families, and this is in accordance with the findings of other investigators (Rosenthal and Duke, 1967, Gordon *et al.*, 1969, Juberg *et al.*, 1975). Though there was parental consanguinity, the parents seemed normal and they had normal and affected offsprings. Moreover, males and females were equally affected, while as far as could be ascertained the relatives of the parents did not display the described anomalies. It may be of interest to note that all previously reported cases of lipoid proteinosis but 1 (Jensen *et al.*, 1972) have been of German extraction, including those found in South Africa (Gordon *et al.*, 1969). Our pedigree is of Jewish-Iranian origin. It is well documented that among the Jewish-Iranian community the rate of consanguinity is as

high as 17.5% for first cousins and 26.3% for overall consanguinity (Goldschmidt *et al.*, 1960). As these families originated from the same small village, this high rate of consanguinity adds more evidence to our hypothesis of an autosomal recessive mode of inheritance.

One of the most intriguing questions in diseases with recessive inheritance is whether one can identify the carrier, the heterozygote for the trait, by detecting early signs of the disease. It seems that the laryngoscopic findings in Case III 3 and the premature total loss of dentition in Case III 6 may be considered as microsigns of the heterozygous state. It is obvious, however, that not every heterozygote can be detected phenotypically with certainty.

As it is generally true that most recessively inherited diseases tend to result from enzyme defects (McKusick, 1972), and as this syndrome is due to a metabolic disturbance, an extensive investigation was carried out to find a possible specific biochemical phenotype. But the laboratory results were all normal, being in accordance with previous reports (Muirhead and Jackson, 1963, Jensen *et al.*, 1972; Burnett and Marcy, 1963).

Since the complete clinical syndrome was not delineated until Blodi's report (Blodi *et al.*, 1960), the likelihood is that the prevalence of the ocular involvement in lipid proteinosis is more widespread than currently appreciated.

The authors acknowledge the kind assistance of Dr Elliot Berry.

References

- Blodi, F. C., Whinery, R. D., and Hendrides, C. A. (1960). Lipoid proteinosis (Urbach-Wiethe) involving the lids. *Transactions of the American Academy of Ophthalmology and Otorhinology*, **58**, 155–166.
- Burnett, J. W., and Marcy, S. M. (1963). Lipoid proteinosis. *American Journal of Diseases of Children*, **105**, 81–84.
- Caplan, R. M. (1967). Visceral involvement in lipid proteinosis. *Archives of Dermatology*, **95**, 149–155.
- Goldschmidt, E. A., Ronen, A., and Ronen, J. (1960). Changing marriage systems in the Jewish communities of Israel. *Annals of Human Genetics*, **24**, 191–197.
- Gordon, H., Gordon, W., and Botha, V. (1969). Lipoid proteinosis in an inbred Namaqualand community. *Lancet*, **1**, 1033–1035.
- Hewson, G. E. (1963). Lipoid proteinosis (Urbach-Wiethe syndrome). *British Journal of Ophthalmology*, **47**, 242–245.
- Jensen, A. D., Khodadoust, A., and Emery, J. M. (1972). Lipoid proteinosis. *Archives of Ophthalmology*, **88**, 273–277.
- Juberg, R., Winder, P. R., and Turk, L. J. (1975). A case of hyalinosi cutis et mucosae with common ancestors in four remote generations. *Journal of Medical Genetics*, **12**, 110–112.
- Katznelson, J., and Ungar, H. (1957). Lipoid proteinosis (reinvestigation of a case previously reported by Urbach and Wiethe in 1929). *Dermatologica*, **115**, 23–35.
- McKusick, V. A. (1972). *Heritable Disorders of Connective Tissue*, 4th edn., p. 5. Mosby: St. Louis.
- Muirhead, J. F., and Jackson, P. (1963). Lipoid proteinosis (of Urbach-Wiethe). *Archives of Ophthalmology*, **69**, 174–179.
- Rosenthal, A. R., and Duke, J. R. (1967). Lipoid proteinosis: case report of direct lineal transmission. *American Journal of Ophthalmology*, **64**, 1120–1125.
- Urbach, E., and Wiethe, C. (1929). Lipidosis cutis et mucosae. *Virchows Archiv für pathologische Anatomie und Physiologie und für klinische Medizin*, **273**, 285–319.