



ORIGINAL ARTICLE

Lipoid proteinosis: A case report with recurrent parotitis and intracranial calcifications

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Abstract Lipoid proteinosis is an autosomal recessive disease of abnormal deposition of glycoprotein in various tissues. Symptoms may include a hoarse voice, lesions and scarring on the skin, easily damaged skin with poor wound healing, dry, wrinkly skin, and beading of the papules around the eyelids. Calcifications of brain tissue can lead to epilepsy and neuropsychiatric abnormalities. In this paper we will review the current literature on the disease and report a case of a 15 year old Saudi female with lipoid proteinosis that presented initially with recurrent parotitis.

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1. Review of the literature

Lipoid proteinosis (also named hyalinosis cutis et mucosae, lipoidosis cutis et mucosae, or Urbach-Wiethe disease) is an autosomal recessive disease of abnormal deposition of glycoprotein in various tissues, most notably skin and mucous membranes, although the brain and other internal organs may also be affected (Gorlin, 1969; Hamada et al., 2002; Chan et al., 2007). The disease is caused by reduced expression of the extra-

cellular matrix protein 1 gene, ECM1, on chromosome 1q21 (Hamada et al., 2002; Chan et al., 2007). There is an increase in mRNA for Type IV procollagen resulting in underproduction of fibrous collagens and overproduction of basement membrane collagens, which tend to deposit in the skin and various organs, which is the characteristic feature of the disease (Rajendran and Sivapathasundharam, 2009).

It is described in the literature as rare (Uchida et al., 2007; Javeria et al., 2008; Santana et al., 2010), however there is a higher prevalence of the disease in populations where it is common to have consanguineous parents (Baykal et al., 2007; Chan et al., 2007; Al-Aboud and Al-Natour, 2008; Al-Natour 2008; Javeria et al., 2008), which may explain the frequent finding in the Saudi population. The South African population also has a relatively higher prevalence of the disease due to the *founder effect* after the introduction of the mutation into the country by a German settler (Chan et al., 2007).

In clinical practice, lipoid proteinosis is rarely a life-threatening condition, and although autopsy studies have shown it to be a generalized disorder with microscopic deposits of hyaline material in practically every organ, symptoms related to the viscera have not been described (Di Giandomenico et al., 2006). Although its features are variable, the disease is characterized

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predominantly by hoarseness of the voice and flesh-colored papules and nodules involving the skin and mucosa (Gorlin 1969; Hamada et al., 2002; Di Giandomenico et al., 2006; Chan et al., 2007).

Hoarseness of the voice, which is usually the first sign of the disease, may present as an inability of infants to cry at birth, or may develop soon after birth, but occasionally may develop after some years. The hoarseness is due to nodules being deposited in the epiglottis and larynx. Rarely, severe cases may develop dyspnea, leading to death in some cases (Leonard et al., 1981; Ozbek et al., 1994; Bazopoulou-Kyrkanidou et al., 1998; Di Giandomenico et al., 2006). The classic and most easily recognizable sign of intradermal nodules is beaded eyelid papules. The involvement of the eyelids may be followed by loss of cilia. Deposition of the nodules may also involve the skin of the face, neck, hands, axilla, scrotum, perineal areas and intergluteal cleft. Hyperkeratotic lesions may present on areas exposed to extension and flexion such as the hands, knees, elbows, and proximal interarticular surfaces of the fingers (Gorlin 1969; Hamada et al., 2002; Chan et al., 2007; Uchida et al., 2007). Rarely, the hyaline deposits may also cause ophthalmic abnormalities (Chan et al., 2007; Mandal et al., 2007), and obstruction of the nasolacrimal duct (Ostrovsky et al., 2007). Photosensitivity may also be associated with this condition (Chan et al., 2007). In some cases the mucocutaneous lesions may manifest as vesiculobullous lesions, which later become erosive, and may heal by scarring (Rao et al., 2008; Bahhady et al., 2009).

Intraorally, the deposits are usually very marked, involving much of the oral mucosa (Chan et al., 2007), and usually appear before puberty and gradually increase in severity. The lips may be thickened due to the deposits and the tongue may be thick and firm to palpation with loss of the dorsal papilla (Gorlin 1969; Neville et al., 2002). Infiltration of the lingual mucosa causes thickening of the sublingual frenum, limiting tongue movements and causing speech difficulties (Di Giandomenico et al., 2006; Chan et al., 2007). The buccal mucosa may have a cobblestone appearance and be firm to palpation (Gorlin 1969; Hamada et al., 2002; Neville et al., 2002). Other oral manifestations may include gingival hypertrophy, xerostomia, and dysphagia (Bazopoulou-Kyrkanidou et al., 1998; Di Giandomenico et al., 2006; Chan et al., 2007; Uchida et al., 2007), as well as congenital absence of the teeth and enamel hypoplasia (Gorlin 1969; Neville et al., 2002). Recurrent ulceration associated with the xerostomia in lipid proteinosis has been reported (Sargenti Neto et al., 2009). The findings of a hoarse voice and an inability to fully protrude the tongue are the most reliable clinical diagnostic features of lipid proteinosis (Chan et al., 2007).

Recurrent inflammation of the parotid and submandibular glands may also occur, due to stenosis of the parotid duct by the surrounding deposits, and there have been reports of reduced salivation and dryness of the mouth associated with lipid proteinosis (Chan et al., 2007; Neville et al., 2002). Some of the patients developed progressive dryness of the mouth in the fourth and sixth decades of life (Disdier et al., 1994; Aroni et al., 1998), while others have noticed it earlier on in childhood (Bazopoulou-Kyrkanidou et al., 1998).

Intracranial and neural involvement are other frequently encountered features of lipid proteinosis. Bilateral, circumscribed, and symmetrical calcifications in the medial temporal regions, lateral to the sella turcica, are common (Leonard

et al., 1981; Ozbek et al., 1994; Siebert et al., 2003; Thornton et al., 2008). However the incidence of such calcifications is difficult to estimate as only a limited number of affected subjects undergo brain imaging (Chan et al., 2007). High-resolution CT examination of the intracranial calcifications in two affected siblings revealed a bony structure consisting of cortical and medullar components (Ozbek et al., 1994), therefore it was suggested that the term "ossifications" should be used instead of "calcifications". The osseous nature of these lesions is supported by the fact that the ECM1 gene is thought to have a role as a negative regulator of endochondral bone formation, inhibiting alkaline phosphatase activity and mineralization (Hamada et al., 2002).

Although this disease is well documented in the medical literature, it is not widely recognized in the dental field. Furthermore, although recurrent parotitis is a common feature of this disease (Chan et al., 2007) we have been unable to find a documented description of the CT appearance of the parotid gland or sialography findings in affected individuals with repeated parotitis. Therefore, we report the clinical findings in Saudi siblings with lipid proteinosis, and the panoramic, CT, and sialography findings from one of the siblings whose chief complaint was recurrent parotitis.

2. Case report

2.1. Clinical features

2.1.1. Sibling 1

A 15 year old female was referred to the Oral and Maxillofacial Radiology (OMFR) clinic by a maxillofacial surgeon for sialography of the left parotid gland to investigate glandular function after repeated episodes of acute infection of the gland. The patient had a history of three episodes of acute infection occurring within a six month period, and the latest was associated with suppuration which was drained intraorally by probing Stensen's duct. Afterward, a localized swelling developed in the left cheek. The swelling was incised and found to contain saliva.

When the patient presented to the OMFR clinic, the initial presenting feature was hoarseness of the voice. A scar was noted in her left cheek and pus could be expressed from the left Stensen's duct. Reduced, viscous saliva was expressed from the right duct. The patient also had dermal papules in her eyelids and widespread submucosal nodules in the mucous membranes of the buccal mucosa, tongue, and lips (Fig. 1a and b). Multiple missing teeth were noted with bad oral hygiene and high carious activity in the existing teeth. Antibiotics and saline mouth rinses were prescribed to control the acute phase of the infection prior to attempting sialography.

2.1.2. Sibling 2

The patient was the offspring of consanguineous parents, and there was a history of mucosal abnormalities in her older sister and younger brother, as well as a maternal uncle. Therefore, the family was requested to undergo clinical examination, however only her younger brother was brought in for examination because the parents stated that only the younger brother exhibited marked mucosal abnormalities. The older sister had a history of hoarseness of the voice which resolved after endoscopic removal of nodules on the vocal cords. According



Figure 1 Submucosal nodules in the mucous membranes of the buccal mucosa (A) and the tongue, and lips (B) of sibling 1.

to the parents, the older sister had no other signs or symptoms. However, confirmation was not possible because the parents deemed it unnecessary to have her examined. Clinical examination of the younger brother revealed papules in the proximal interarticular surfaces of his fingers and more marked infiltration of the tongue and buccal mucosa than seen in his sister. Hypertrophy of the gingiva was also noted. However, he exhibited no hoarseness of the voice. During the examination, the brother was noted to suffer from photosensitivity and was irritable. Milking of all major salivary glands elicited saliva of normal quantity and quality.

2.1.3. Radiographic features

After the acute infection subsided, sialography was performed. The radiographic examination consisted of a panoramic radiograph, sialographic views, and CT. The sialographic views included lateral oblique and frontal views of the left side of the mandible before and after introduction of the contrast agent. The CT images were postcontrast axial and coronal sections of the head and neck which had been previously obtained by the surgeon during one of the parotitis episodes.

The panoramic radiograph (Fig. 2) revealed delayed dental development; and three of the second permanent molars had still not fully erupted. Multiple teeth were congenitally missing, which were the upper lateral incisors, all of the second premolars and third molars, with retained primary upper canines and primary second molars. An amorphous radiopaque lesion was also noted in the region of the right maxillary tuberosity. The lesion was approximately 1 cm in diameter with a radiolucent rim and a well defined and corticated margin. It was seen to slightly expand the distal border of the tuberosity, and no evidence of perforation of cortical boundaries was detected. No effect on the adjacent tooth was noted. The lesion was

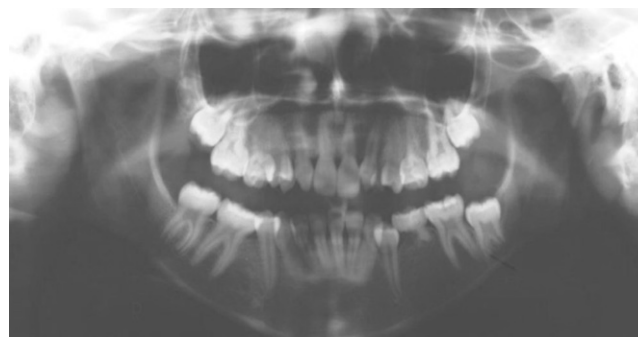


Figure 2 Panoramic radiograph of sibling 1 (15 years old female) showing delayed dental development, unerupted molars, congenitally missing permanent teeth, retained primary teeth.

diagnosed as a complex odontome. The history and clinical appearance, combined with the panoramic radiographic findings, were suggestive of lipoid proteinosis.

The sialographic exam (Fig. 3A and B) revealed escape and pooling of the contrast media buccal to the main duct with abnormal shape of the peripheral ducts. The ductal tree branches were found to be thin and reduced in number. There was incomplete emptying of the contrast media even after a 30 min stimulated post-evacuation period. On a recall visit one week later, no contrast agent was detected on a lateral oblique film. The patient reported post-examination swelling and redness in the area and eye irritation that disappeared on the same day. The sialographic impression was that of altered ductal structure of the left parotid gland. The escape and collection of contrast agent from the main duct were likely due to perforation of the Stensen's duct during pus draining.

A review of the CT images (soft tissue window) of the parotid glands revealed increased radiodensity of both glands, isodense to that of muscles (Fig. 4A and B). Axial sections also revealed reduced medio-lateral dimension of the glands, and loss of the normal heterogeneity of the internal structure of both glands. The larynx was visible in the available image sections, and no papules could be detected on the surface of the

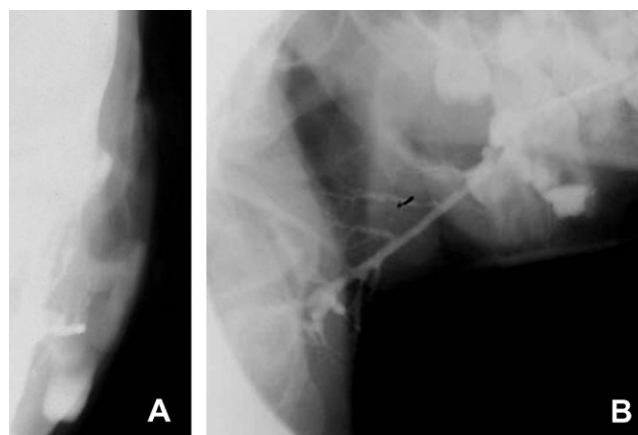


Figure 3 Sialographic views (PA mandible and lateral oblique) of the left parotid gland revealed escape and pooling of the contrast media buccal to the main duct (A) with abnormal dilated peripheral ducts (B).

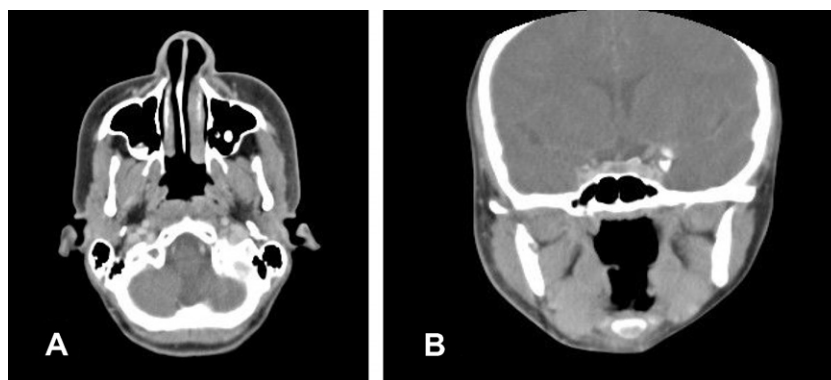


Figure 4 Axial (A) and coronal (B) CT images (soft tissue window) of the parotid glands.

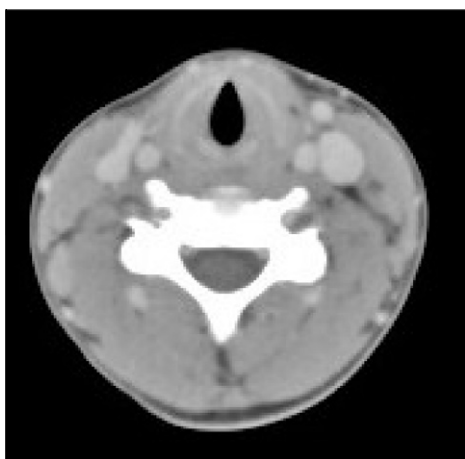


Figure 5 Axial CT image (soft tissue window) of the larynx did not show any papules on the surface of the vocal cords.

vocal cords (Fig. 5). Additionally, the brain was also visible in the CT sections, and both hard and soft tissue windows clearly demonstrated bilateral calcifications lateral to the sella turcica (Fig. 6A and B). The coronal sections from the hard tissue window demonstrated two separate calcifications on either side of the sella turcica. The larger, superior calcified bodies had a slightly variable radiodensity with the medial apex being slightly more dense than the rest of the calcified mass. However, the entire mass had a radiodensity greater than that of trabecular bone, but less than that of cortical bone.

2.1.4. Histomorphological features

Incisional biopsy of the lower labial mucosa was performed, and histopathological examination with H&E stain revealed periglandular acellular material which blended with the nearby collagenous fibers. At some deeper foci, there appeared to be denaturing of the collagen fibers to produce basophilic or “fibrinoid” degeneration. No inflammation was detected (Fig. 7A and B). The appearance was not diagnostic, and since the clinical information indicated a case of lipid proteinosis, PAS stain and diastase was requested to help clarify the nature of the suspicious periglandular material. The resulting slides showed the slightly bluish colored denatured collagen (or glycoprotein) seen in H&E stain to be magenta in color with PAS stain, and to resist digestion by diastase. It was presumed to be the lesional

glycoprotein (Fig. 8A and B). The histopathological diagnosis was, therefore, consistent with lipid proteinosis.

2.1.5. Follow-up

After the diagnostic workup of the patient and conservative treatment of the parotitis, the family was advised on the need for long-term care of the oral condition for all the affected siblings, but the family refused further intervention. The family was contacted five years later, and the mother stated that the first sibling has not had another parotitis episode since then.

3. Discussion

Although the definitive diagnosis of lipid proteinosis can only be achieved by genetic analysis, the clinical features of the condition may be highly suggestive in some cases, and may be reinforced by imaging findings. The presence of hoarseness of the voice, submucosal deposits, eyelid papules, recurrent parotitis, and a positive familial history in the first sibling who presented to us suggested the possibility of the disease. Congenital absence of multiple teeth and intracranial calcifications, detected on panoramic and CT images respectively, reinforced the diagnosis. The histopathological appearance of periductal deposits of PAS positive, diastase resistant, glycoprotein was also consistent with a diagnosis of lipid proteinosis.

The relatively high rate of consanguineous marriage in Saudi Arabia increases the likelihood of a dentist encountering a case of lipid proteinosis. Although, to our knowledge, there are no published studies on the prevalence of this disease in the Saudi population, the expected higher prevalence may be highlighted by the fact that identification of the gene mutation causing the disease was achieved using the DNA of the affected members of a Saudi family (Hamada et al., 2002). Dentists practicing in Saudi Arabia should, therefore, be familiar with the clinical and radiographic features of the disease for a timely diagnosis and proper understanding of the cause and pathogenesis of any associated abnormalities.

The cases presented here highlight the variable clinical presentation of the disease, probably due to incomplete penetrance, even within the same family. For although a hoarse voice and inability to fully protrude the tongue are considered the most reliable clinical diagnostic features of lipid proteinosis (Chan et al., 2007), neither sibling in our report displayed both features. For while the sister presented with severe hoarseness of the voice, eyelid papules, mucosal deposits,

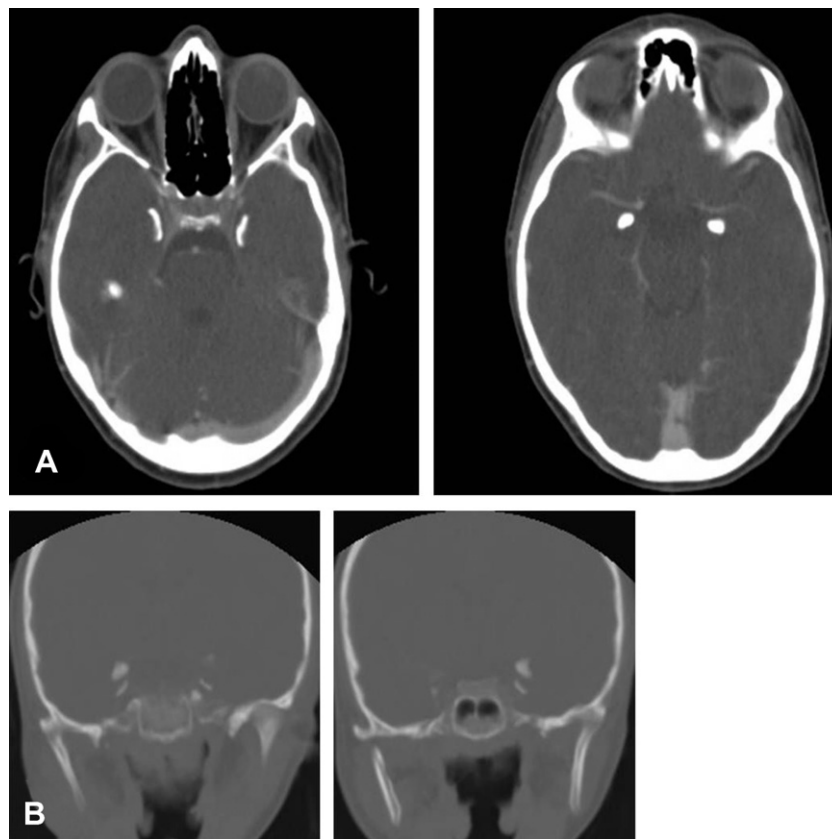


Figure 6 Axial (A) and coronal (B) CT images of the brain demonstrated bilateral calcifications lateral to the sella turcica.

and recurrent parotitis, the brother presented with more marked mucocutaneous manifestations and photosensitivity, and no hoarseness of the voice.

Although the sister suffered from considerable hoarseness, with her speech being inaudible at times, we were unable to detect any laryngeal changes on CT examination of the larynx. This is in contrast to the findings of [Ozbek et al. \(1994\)](#), who detected thickening and nodularity in most of the laryngeal structures of their patients (who suffered from hoarseness of the voice). Our findings may possibly be due to the thickening and nodularity being restricted to within the vocal cords, and not manifesting as nodules on the surface. If such was the case, then the difference in CT radiodensity of the affected and unaffected areas may not be sufficient to be visualized on the CT images. Of interest to note is that the brother, who had more marked mucocutaneous deposits, did not suffer from hoarseness of the voice.

Regarding the intracranial calcifications, it could not be concluded from the CT images of our patient whether the intracranial calcifications were osseous in nature or not. The radiodensity of the masses does not seem to indicate either trabecular or cortical osseous structures. This is in contrast to [Ozbek et al. \(1994\)](#), who reported that high-resolution CT images of the intracranial calcifications revealed a bony structure consisting of both cortical and medullar components ([Ozbek et al., 1994](#)). And although [Appenzeller et al. \(2006\)](#) have stated that intracranial calcifications are more evident in patients with longer disease duration ([Appenzeller et al., 2006](#)), our female patient was found to have clearly established calcifications at the age of 15 years. Furthermore, she had no

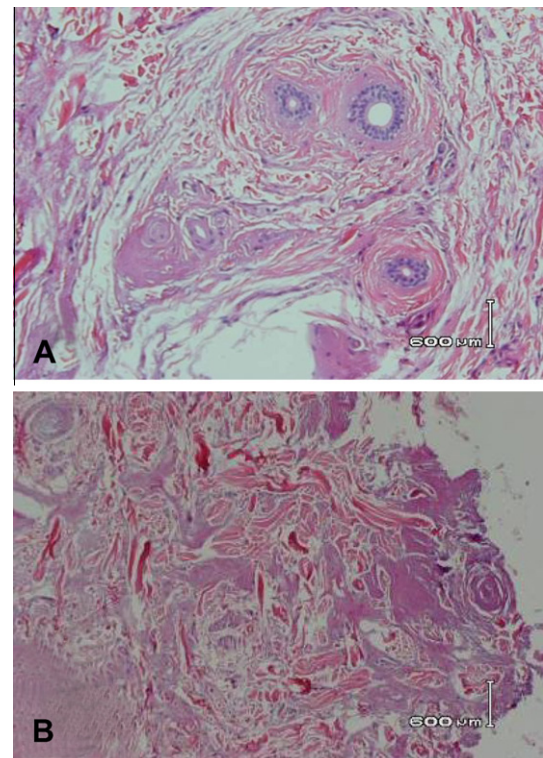


Figure 7 Histopathological slides in H&E stain (A and B) of an incisional biopsy of the lower labial mucosa revealed periglandular acellular material which blended with the nearby collagenous fibers.

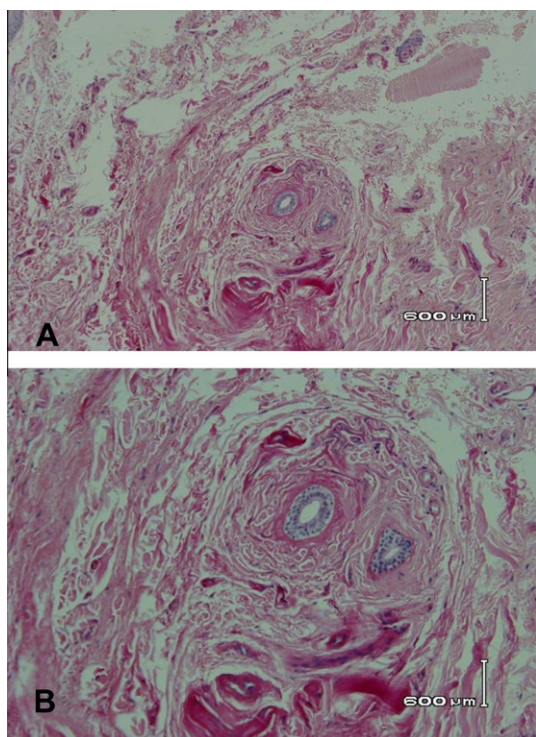


Figure 8 Histopathological slides (PAS stain and diastase) of an incisional biopsy of the lower labial mucosa in low power (A) and high power (B) showed the bluish colored denatured collagen seen in H&E to be magenta in color and to resist digestion by diastase.

history of epilepsy at the time of examination, which does not contrast with the findings of Appenzeller et al. (2006) who have concluded that epilepsy, when present, may be related to the intracranial calcifications. Their findings do not indicate that epilepsy is always associated with intracranial calcifications. But rather, that the damage caused by the calcifications is what may cause the epilepsy.

The degree to which the emotions and memory functions were affected in our patients was not fully assessed, but the interactive skills of both siblings were judged by the authors to be abnormal to a certain degree. The parents, however, gave a history of unimpaired mental performance of their children. No neuropsychological tests were performed, however, for a controlled evaluation of their emotional and memory skills.

Regarding salivary gland function of the sister, the clinical examination revealed reduced salivary flow from the asymptomatic parotid gland and complete absence in the symptomatic gland, yet the patient did not complain of xerostomia. A possible reason for the repeated parotitis episodes may be stricture of Stensen's duct (as a result of the deposits in the buccal mucous membranes) which may cause retrograde infections (Gorlin, 1969; Neville et al., 2002). However, the abnormal ductal tree morphology detected with sialography, and the viscous consistency of the saliva from the asymptomatic right gland may indicate that changes within the structure of the gland itself may precede any acute inflammatory episodes. A possible reason for cessation of the parotitis episodes in our patient may be that the stricture of Stensen's duct was eliminated with the dilation and cannulation of the duct during the sialography procedure.

Although the patient had repeated inflammation of the parotid gland, the histomorphological findings indicated absence of inflammation because the sample was taken from the lower lip, which was not associated with the inflammation.

Although in some cases, the disease may be associated with serious manifestations, and although the recurrent parotitis of the sister was causing much concern to her parents, the parents did not consider this systemic condition as serious. Therefore, genetic counseling should be provided for affected families even if the affected members feel they are only slightly affected by the disease; for future offspring may develop even more serious manifestations.

4. Conclusion

Although a provisional diagnosis of lipid proteinosis can usually be reached by history and clinical examination, radiographs of the jaws can help determine the extent of dental abnormalities, while CT and sialographic examinations can the diagnostic accuracy of the disease. Dentists practicing in Saudi Arabia should be aware of this disease and its oral implications in order to refer the afflicted patients for the necessary medical management, and to provide them with the optimum dental care.

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