

Minor salivary gland biopsy for the diagnosis of familial amyloid polyneuropathy

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Abstract The diagnosis of Val30Met familial amyloidotic polyneuropathy (FAP) is based on genetic tests, clinical manifestations, familial history and biopsy of peripheral tissues (e.g. rectum, abdominal fat pad, sural nerve, and minor salivary gland) to confirm the presence of amyloid deposits. The aim of this study was to determine the frequency of amyloid deposits in minor salivary glands biopsied from FAP patients and to investigate whether an association exists between the presence of these deposits and clinical features. Seventeen patients with FAP were submitted to minor salivary gland biopsy to confirm the presence of amyloid deposits. The histopathology of the salivary glands confirmed glandular amyloid deposits in nine symptomatic patients (sensitivity of 75.0%). In general, FAP patients who tested positive for glandular amyloid deposits exhibited significantly higher frequencies of sensorimotor and dysautonomic dysfunctions ($p = 0.001$) compared with those who tested negative. None of the patients reported xerostomia. Minor salivary gland biopsy may help confirm the diagnosis of FAP in symptomatic cases, as it is noninvasive, easy to execute, and causes minimal discomfort to patients.

Keywords Transthyretin mutation · Familial amyloidotic polyneuropathy · Minor salivary gland biopsy

Introduction

Familial amyloidotic polyneuropathy (FAP) is an autosomal dominant disorder which varies in penetrance. The FAP derived from mutations in the transthyretin gene (TTR) is mostly common and TTR Val30Met is the most frequent substitution mutation [1, 2], being frequently reported in Portugal [3], Brazil [4], Sweden [5], and Japan [6].

The Val30Met FAP can vary in phenotype depending on the tissue involved in the amyloidosis. The first clinical symptoms manifest in adult patients as they report discomfort in the feet, mainly numbness, decrease in thermal and pin-prick sensations, and spontaneous pain. With the progression of the disease, neurological deficits extend to the legs and upper limbs, causing motor dysfunction which affects walking and lead to muscle loss. Orthostatic hypotension, post-prandial diarrhea or constipation, vomiting, erectile dysfunction, dysuria, and urinary retention are some of the autonomic alterations frequently reported. Progressive amyloid deposition can cause cardiomyopathies, ocular abnormalities, and progressive renal failure [1, 7]. Liver transplantation is accepted as a treatment option for the disease. This procedure eliminates the main source of mutated TTR, leading to decline in its serum levels and consequent interruption of FAP progression [8].

The TTR–FAP diagnosis is based on neurological and autonomic symptoms, including TTR gene sequencing for detecting the mutation and family history of neuropathy [1]. Histopathological analysis of peripheral tissues for detecting amyloid deposits is recommended for all patients

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[7]. These tissues are the sural nerve, abdominal subcutaneous adipose tissue, rectum, kidneys, skin, gastric mucosa, and salivary glands [7]. Aspiration of subcutaneous adipose tissue is considered the most common diagnostic method for systemic amyloidosis due to its low cost and ease of technical execution [9]. Biopsy of minor salivary glands in the labial mucosa is considered an alternative method to adipose tissue biopsy, mainly due to easy access of these glands and rapid rate of mucosa regeneration. Studies have demonstrated that salivary gland biopsy has high sensitivity and specificity for diagnosis of systemic amyloidosis (Table 1), and other investigations have concluded that it is a good method to confirm FAP [11, 15]. During the process of FAP diagnosis, salivary gland biopsy has been indicated mainly due to the fact that some patients with autonomic dysfunctions exhibit normal electromyography tests, and the detection of amyloid deposits in the salivary gland may confirm the diagnosis of FAP. In addition, not all patients who are positive for the Val30Met mutation will develop the disease, as the gene penetration is not 100% [1, 4]. Therefore, salivary gland biopsy is a complementary diagnostic tool for electromyography and genetic tests, mainly in the case of the presence of autonomic disturbances [1].

The aim of this study was to determine the frequency and histopathological characteristics of amyloid deposits in minor salivary glands biopsied from FAP patients who attended a Brazilian liver transplantation centre. Clinical data on symptoms, signs, and stages of FAP were also collected to investigate whether an association exists between clinical features and presence of amyloid deposits in minor salivary glands.

Materials and methods

The methodology described below was previously approved by the Research Ethics Committee of the Hospital Israelita Albert Einstein in July 2015 (Project #2138-14). The study was performed in accordance with the Helsinki declaration.

Patients and methods

This study is a description of FAP cases which were indicated for liver transplantation at the Hospital Israelita Albert Einstein, Brazil. The patients were selected based on the following inclusion criteria: positive genetic diagnosis of TTR Val30Met mutation [detected by deoxyribonucleic acid (DNA) sequencing]; electromyography of the lower limbs; and salivary gland biopsy for detection of amyloid deposition. The severity of the disease was established through neurological evaluation. All FAP patients

undergoing histopathological analysis of the salivary gland were included in the study. Patients whose genetic diagnoses did not confirm FAP and those whose clinical data were not sufficient enough to determine the disease stage were excluded from the study. The selected patients signed an informed consent form in which they agreed with the use of their medical information by future studies. Because this was a retrospective study, the local research ethics committee approved the methodology based on the patients' previous informed consent form.

Clinical data collection

The following clinical data were retrieved from the selected patients' medical records: gender, age when attending the liver transplantation center, age at onset of the disease symptoms, relatives with the same disease, country of origin and family ancestry, results of electromyography exams, and symptoms related to sensorimotor neuropathies and autonomic dysfunctions of the cardiovascular, gastrointestinal, genitourinary, buccal (dry mouth sensation), and ocular (dry eyes and decrease of visual acuity) systems.

Severity grading for clinical symptoms and signs

A severity grading of neurological and autonomic dysfunctions was adopted for classifying a patient's disease stage. This system was established by Coutinho et al. [19], and includes the following scores [7]: stage 0—asymptomatic patient; stage I—patient with mild sensory, motor or dysautonomic symptoms in the lower limbs, but unimpaired ambulation; stage II—moderate impairment progression to the lower limbs, upper limbs, and trunk; necessity of assistance for ambulation; and stage III—wheelchair-bound or bedridden; severe sensory, motor, and autonomic involvement of all limbs.

Salivary gland biopsy and histopathological analysis for amyloid deposits

The patients were submitted to minor salivary gland biopsy in the labial mucosa under local anesthesia. A small incision was performed in the middle region of the inferior lip, and an entire minor salivary gland was carefully dissected and removed. The specimen was then fixed in formalin and sent for histopathological examination.

Amyloid deposits were microscopically diagnosed as being a hyaline material present in histological slices stained with hematoxylin and eosin. The amyloid deposition was confirmed using Congo red stain. Cases with green bi-refringence under polarized light were considered positive for amyloid deposits.

Table 1 Results reported in the literature on sensitivity and specificity of some periphery tissue biopsies for systemic amyloidosis diagnosis (articles in chronological order)

Type of amyloidosis and total number of cases (<i>n</i>)	Analyzed tissues	Sensitivity and specificity	Study conclusion	Ref.
Secondary amyloidosis due inflammatory conditions (<i>n</i> = 19)	Labial salivary gland Gingiva	Labial salivary gland Sensitivity = 100.0% Gingiva Sensitivity = 15.79	Labial salivary gland proved to be a valuable method for the diagnosis of secondary amyloidosis	[10]
Primary and secondary amyloidosis due to plasma cells dyscrasia and inflammatory conditions (<i>n</i> = 59)	Labial salivary gland	Sensitivity = 86.0% Specificity = 100.0%	Labial salivary gland biopsy has high sensitivity for primary and secondary amyloidosis, and should be performed when amyloidosis is suspected	[11]
Senile systemic amyloidosis (<i>n</i> = 100)	Abdominal fat pad compared with labial salivary gland	Abdominal fat aspiration Sensitivity = 75.0% Specificity = 87.5% Minor salivary gland biopsy Sensitivity = 100.0% Specificity = 99.9%	Salivary gland biopsy seems to be more reliable test than abdominal fat pad aspiration for the diagnosis of primary and secondary amyloidosis in elderly	[12]
Familial amyloid polyneuropathy (<i>n</i> = 32)	Labial salivary gland	Sensitivity = 100.0% Specificity = 96.0%	Labial salivary gland biopsy is a sensitive and specific test for amyloid neuropathy diagnosis	[13]
Primary amyloidosis, including FAP Secondary amyloidosis due to neoplasms and inflammatory conditions (<i>n</i> = 45)	Abdominal fat pad	Sensitivity = 58.0% Specificity = 100.0%	Abdominal fat pad aspiration has excellent sensitivity and specificity for systemic amyloidosis	[9]
Secondary amyloidosis due neoplasms and inflammatory conditions (<i>n</i> = 297)	Abdominal fat pad (cytology compared with histology)	Sensitivity = 78.0% Specificity = 98.0%	Abdominal fat pad aspiration cytology is a useful screening tool for systemic amyloidosis	[14]
Familial amyloid polyneuropathy (<i>n</i> = 87)	Labial salivary gland	Sensitivity = 91.0% Specificity = not analyzed	Labial salivary gland has a very good sensitivity and should be considered a method of choice for familial amyloid polyneuropathy diagnosis	[15]
Secondary amyloidosis due inflammatory conditions (<i>n</i> = 98)	Labial salivary gland biopsy	Sensitivity = 83.0% Specificity = 100.0%	Labial salivary gland biopsy analyzed with immunofluorescence has high sensitivity for the diagnosis of secondary amyloidosis	[16]
Secondary amyloidosis due inflammatory conditions (<i>n</i> = 35)	Minor salivary gland	Sensitivity = 61.1% Specificity = not reported	Minor salivary gland biopsy is a safe and simple method for systemic amyloidosis evaluation	[17]
Familial amyloid polyneuropathy (cited reports in European consensus for diagnosis, management and treatment)	Sural nerve Labial salivary gland Abdominal fat pad	Sensitivity = 79–80%; Specificity = High Sensitivity = 91%; Specificity = High Sensitivity = 4–83%; Specificity = High	Variation of the biopsy site is dependent of center expertise, including the pathologist experience	[18]

All of the histological slices of the salivary glands were reviewed by a single pathologist, who subjectively attributed intensity scores to the following tissue elements: inflammation, necrosis, periductal amyloid deposits, periacinar amyloid deposits, perivascular amyloid deposits, amyloid deposits in muscles, and peripheral nerve localized in the glandular stroma. The scores were 0 (absent), 1

(discrete, with up to 25% of the microscopic field showing the tissue element), 2 (moderate, with between 25 and 50% of the microscopic field showing the tissue element), and 3 (intense, with more than 50% of the field occupied by the alteration). The microscopic observation was performed at 100× and 400× magnifications. Biopsies from other regions commonly used for amyloidosis diagnosis were

also reviewed to confirm the presence or absence of amyloid deposits.

Statistical test

The clinical and histopathological data were presented as absolute and relative frequencies. The patients were divided into two groups: patients with amyloid deposits in the salivary gland (Group 1) and patients without such amyloid deposits (Group 2). The data from the two groups were compared using Fisher's exact test. The significance level was set at 5%.

Results

Patient characteristics

Thirty-two patients attended the Liver Transplantation Center at the Hospital Israelita Albert Einstein from January 2013 to December 2014. Of these patients, only 17 were submitted to minor salivary gland biopsy for FAP diagnosis, because this procedure had recently been implemented in our service. All the 17 patients were included in the study. In nine patients (52.9%), amyloid deposits were found in the glandular parenchyma and stroma and eight patients (47.1%) were negative for these deposits.

The clinical characteristics of the FAP patients who underwent salivary gland biopsies are shown in Table 2. The frequency between males and females was similar, and the median age at diagnosis was 31 years. Parental transmission was derived from their mother's and father's relatives with similar frequencies. The presence of disease was reported for up to two prior generations. All the families originated from Portugal, whereas the relatives were all born in Brazil.

Sensorimotor manifestations and autonomic dysfunctions

Sensorimotor manifestations were observed exclusively in the lower limbs, with exception of one patient who exhibited pain in both upper and lower limbs (Table 2). Based on a comparison between the patients of Groups 1 and 2 (with and without amyloid deposits in the salivary gland, respectively), the former group exhibited a higher frequency of pain associated with sensorimotor alterations compared to the latter (Fisher's exact test, $p = 0.001$). Walking difficulties, weakness, and muscle wasting were not detected in either group. With regard to autonomic dysfunctions, the highest frequency was of gastrointestinal manifestations, followed by cardiac and genitourinary alterations (Table 2). Based on a comparison between the

groups regarding autonomic dysfunctions, only Group 1 exhibited genitourinary disturbances (Fisher's exact test, $p = 0.029$). Overall, only four patients showed body mass loss, and none of the patients reported dry mouth or dry eyes (Table 2).

Clinical severity of familial amyloid polyneuropathy

Based on the symptoms of sensorimotor dysfunctions, each patient was assigned a severity score of the disease. Table 3 shows the number of patients assigned to each score level. All the patients with amyloid deposits in the salivary gland were assigned to stage I (9/17, 52.9%). The patients without such deposits were assigned to stages 0 (5/17, 24.9%) and I (3/17, 17.6%). There were no patients with stages II and III.

Electromyography exams

Table 3 shows the findings in the electromyography exams. Nine patients (52.9%) had no abnormalities, and six (35.3%) exhibited symmetric impairment of sensitive and motor fibers in the distal portion of the lower limbs, suggesting incipient polyneuropathy. Mild-to-moderate impairment of the nerves of the carpal tunnel was also observed in three (17.6%) patients. Of these, one exhibited erectile dysfunction and amyloid deposits in the salivary gland. The other two patients did not exhibit amyloid deposits in the salivary gland; one showed neuropathy in the lower limbs, and the other had no symptoms. All the patients with impairment of the nerves of the carpal tunnel were kept under observation until their clinical conditions worsened.

The patients with no abnormalities in the electromyography exam were at stage 0 ($n = 5$) and stage I ($n = 4$) of the disease severity. In addition, the majority with normal electromyography exam did not exhibit amyloid deposits in the salivary gland. On the other hand, in the group with amyloid deposits, electromyography exams showed that the frequency of the absence of abnormalities and suggestion of polyneuropathy were equal.

Histopathological findings in minor salivary glands

Table 4 shows the histopathological scores for salivary gland alterations. The group without amyloid deposits in the labial salivary glands showed no inflammation, necrosis, or other significant alteration. In the group with final diagnosis of amyloid deposits, the salivary glands with hyaline material detected by hematoxylin and eosin stain were submitted to Congo red staining and analyzed under polarized light (Fig. 1a). Material with green bi-refringence was considered positive for amyloid deposits (Fig. 1b). Amyloid deposits were observed surrounding the

Table 2 Clinical characteristics of patients with familial amyloid polyneuropathy submitted to labial salivary gland biopsy ($n = 17$)

Clinical characteristics	
Gender— n (%)	
Male	8 (47.1)
Female	9 (52.9)
Age at the moment of diagnosis—median (range)	31 (26–57)
Relatives with familial amyloid neuropathy— n (%)	
Related to the mother	7 (41.2)
Related to the father	8 (47.1)
Without information	2 (5.9)
Sensory-motor neuropathy—Yes/No— n (%)	16 (94.1)/1 (5.9)
Symptoms and signals in lower limbs	
Only pain	8 (47.1)
Pain, impaired thermal sensibility, and reduction on pin-pick sensation	6 (35.3)
Paresthesia	1 (5.9)
Symptoms in upper and lower limbs	
Only pain	1 (5.9)
Cardiac manifestations—Yes/No— n (%)	
Block of conduction detected by electrocardiogram	2 (11.8)
Orthostatic hypotension/Pre-syncope	2 (11.8)
Genitourinary manifestations—Yes/No— n (%)	
Dysuria	1 (5.9)
Erectile dysfunction/Ejaculatory disturbances	3 (17.6)
Recurrent infection in the urinary tract	1 (5.9)
Gastrointestinal manifestations—Yes/No— n (%)	
Diarrhea	3 (17.6)
Constipation	2 (11.8)
Dyspepsia	1 (5.9)
Body mass loss—Yes/No— n (%)	4 (23.5)/13 (76.5)
Dry mouth/Dry eyes—Yes/No— n (%)	0 (0.0)/17 (100.0)

Table 3 Scores for clinical severity of familial amyloid polyneuropathy based on the stage of sensorimotor dysfunction, and electromyography diagnosis in accordance with the presence or absence of amyloid deposits in salivary glands

	With amyloid deposits in salivary glands ($n = 9$)	Without amyloid deposits in salivary glands ($n = 8$)
Score classification		
Stage 0	0 (0.0)	5 (29.4)
Stage I	9 (52.9)	3 (17.6)
Stage II	0 (0.0)	0 (0.0)
Stage III	0 (0.0)	0 (0.0)
Electromyography diagnosis		
Without abnormalities	4 (23.5)	5 (29.4)
Suggestive of sensorimotor neuropathy in lower limbs	4 (23.5)	1 (5.9)
Impairment of the median nerve of the carpal tunnel	1 (5.9)	2 (11.7)*

See the characteristic of each clinical stage in “[Materials and methods](#)”

* One patient showed alterations in the carpal tunnel associated with sensorimotor neuropathy in lower limbs

Table 4 Histopathological scores (median and range) for salivary gland alterations observed in patients with familial amyloid polyneuropathy submitted to salivary gland biopsy

Histopathological alteration	Group 1—with amyloid deposits in salivary glands ($n = 9$)	Group 2—without amyloid deposits in salivary glands ($n = 8$)
Inflammation	1 (1–2)	0 (0–0)
Necrosis	1 (0–1)	0 (0–0)
Periductal amyloid deposits	0 (0–1)	–
Periacinar amyloid deposits	1 (1–2)	–
Perivascular amyloid deposits	1 (1–2)	–
Amyloid deposits in the muscular fibers	1 (0–2)	–
Amyloid deposits in the peripheral nerve fibers	0 (0–1)	–

0—absent; 1—discrete, up to 25% of the microscopic field showing the tissue element), 2 (moderate, from 25 to 50% of the microscopic field), and 3 (intense, more than 50% of the field occupied by the alteration)

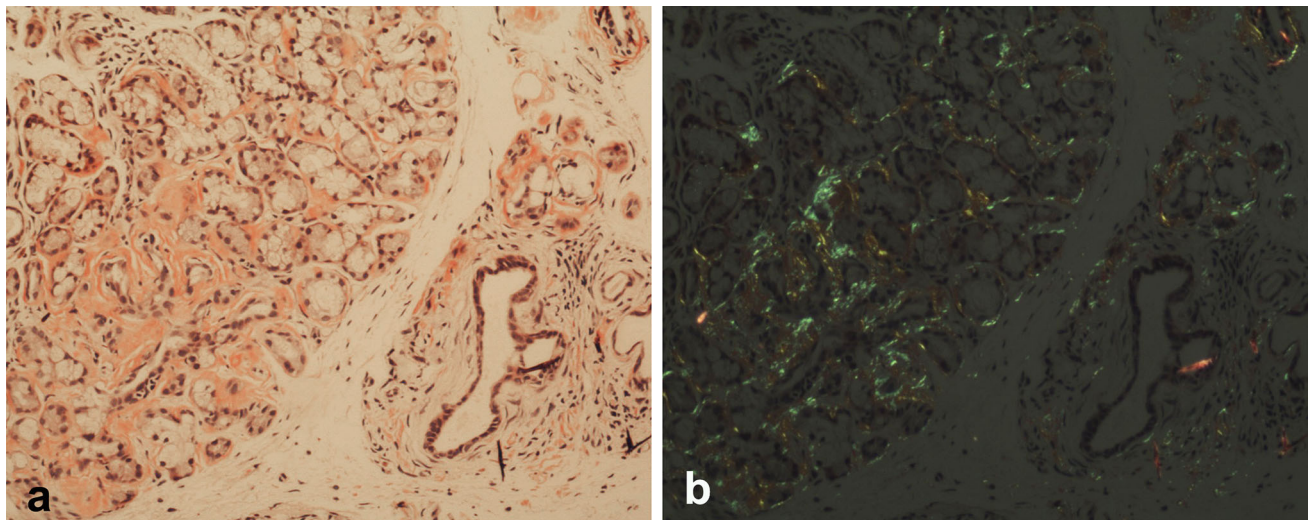


Fig. 1 Histopathological aspect of a minor salivary gland showing amyloid deposits. **a** Presence of hyaline deposits surrounding the acini and in the interstitium (hematoxylin and eosin stain, $\times 400$ original

magnification). **b** Positive bi-refringence under polarized light, confirming the amyloid origin (Congo red stain, $\times 400$ original magnification)

acini and vessels, with a discrete-to-moderate intensity. Periductal amyloid deposits were seen with discrete intensity in only one patient. Amyloid deposits were also observed in the muscle and peripheral nerve fibers present in the salivary gland stroma. In addition, discrete-to-moderate sialadenitis and necrosis were observed in all patients with amyloid deposits in the salivary glands.

Two patients were submitted to sural nerve and duodenum biopsies to detect the presence of amyloid in those organs. No amyloid deposits were detected using histopathological analysis and Congo red staining in either case. Interestingly, one of the patients submitted to sural nerve and duodenum biopsies was positive for amyloid deposits after salivary gland examination.

Sensitivity of the salivary gland biopsy

Patients were considered symptomatic when exhibited sensorimotor and autonomic dysfunctions, i.e., all the patients at stage I of clinical severity ($n = 12$), independently of the electromyography diagnosis. All the patients with amyloid deposits in the salivary gland ($n = 9$) were symptomatic, resulting in a sensitivity of 75.0%.

Liver transplantation

Five patients who tested positive for amyloid deposits in the salivary gland were listed as candidates for liver transplantation. The transplantations were not performed

until the end of the study (October 2015). Four patients in this group were kept under observation until their clinical conditions worsened. Seven of the patients who tested negative for amyloid deposits in the salivary gland were not indicated for liver transplantation until the end of the study. Only one patient in this group was waiting for worsening clinical conditions before undergoing liver transplantation.

Discussion

This descriptive study showed the clinical characteristics of Brazilian FAP patients who underwent minor salivary gland biopsies to detect amyloid deposits in peripheral tissues. To the best of our knowledge, this is the first study to report the usability of the minor salivary gland for the diagnosis of FAP progression in Brazilian patients.

Studies on FAP in Brazilian families are scarce, even though the disease is endemic in this country. Some studies have demonstrated a phenotype similar to that observed in Portuguese patients [20]. The clinical characteristics of the patients described in this study are compatible with those reported in the literature. Data from two large samples of Brazilian TTR–FAP patients [4, 21] showed a mean age of onset in the third decade of life and a mild disease score, with these results being similar to those found in the present investigation.

In this study, we found that all the patients with amyloid deposits in the salivary glands exhibited stage I for FAP severity, but some of them did not exhibit abnormalities in the electromyography exams. Although the number of analyzed patients was very limited, this trend may indicate that amyloid deposits in the salivary glands are present in the mild stages of FAP. However, we have to consider that asymptomatic patients may also present amyloid deposits before the onset of clinical symptoms, which may be detected by other diagnostic tools, such as magnetic resonance neurography [22]. With regard to the salivary gland biopsy, a study [15] in which a larger sample of TTR–FAP patients revealed that 95.7% of the FAP patients diagnosed with mild severity scores showed glandular amyloid deposits, and 18% of the asymptomatic patients showed also such deposits.

An unexpected finding in this study was that patients with genitourinary manifestations were found only in the group with amyloid deposits in the salivary gland. We did not find any physiology explanation for this fact. This association probably occurred, because the majority of the patients with amyloid deposits in the salivary glands were young male adults, with the main genitourinary disturbance being erectile dysfunction without any association with underlying diseases. Therefore, this result may be due to the high frequency of men in this group.

In our sample, the amyloid deposits in the salivary glands were found in 52.9% of the patients, and the sensitivity of the biopsy was 75.0%. This frequency is in accordance with results described in studies analyzing the sensitivity of salivary gland biopsy for the diagnosis of systemic amyloidosis. The sensitivity of salivary gland biopsy in these studies was high (from 61.1 to 100.0%; see Table 1) [10–13, 15–18], being superior to abdominal fat pad aspiration in some cases [12]. In a study with patients who showed chronic sensory and motor polyneuropathy, including TTR–FAP, the sensitivity and specificity of glandular biopsy in detecting amyloid neuropathy were 100 and 96%, respectively, which in some cases were higher than those of sural nerve biopsy [13].

Based on our results and in the literature, we considered that minor salivary gland biopsy may be a useful tool for confirming the diagnosis of the FAP. In addition, this procedure can be indicated for those cases of positive TTR mutation with sensorimotor alterations and autonomic dysfunctions but with normal results in the electromyography exams. This fact is very important in the context of our liver transplantation center, in which it is necessary the confirmation of amyloid deposition for indication for liver transplantation waiting list [7].

Sural nerve, abdominal fat pad, and rectum were the most cited biopsy locations for FAP diagnosis in published scientific papers. However, in an international multicenter TTR–FAP survey performed with 957 symptomatic and asymptomatic patients [3], salivary gland biopsy was the most executed (38% of the 512 biopsies reported). This frequency was probably derived from the fact that a high number of Portuguese patients were included in the study, with salivary gland biopsies being widely adopted in the main Portuguese centers [3]. Gingival and lingual biopsies for diagnosis of systemic amyloidosis were also briefly cited in the literature, but the sensitivity of these techniques seems to be lower than that of glandular biopsies [10].

In the present report, amyloid deposits in the salivary gland had a discrete-to-moderate distribution area, and mild glandular inflammation and destruction were observed. In general, the glandular architecture was found to be preserved. These histopathological findings were quite different from those described in other studies with larger TTR–FAP samples. In the study by Do Amaral et al. [15], a significant frequency of severe glandular destruction was described, including loss of glandular acini, marked interstitial fibrosis, and intense hyalinization of the stroma. Such findings were detected in 63% of the patients, but no xerostomia was found. The authors partially explained the absence of xerostomia by the fact that the preserved acini and ducts exhibited normal ultrastructural appearances, which may be responsible for the secretion of saliva. Another study investigating FAP patients related

xerostomia to glandular amyloid deposits in only one case [13]. We also did not detect any case of xerostomia or other oral alterations. Moreover, it is important to consider that saliva flow is also determined by major salivary glands, which are probably not profoundly affected by the disease.

In conclusion, minor salivary gland biopsy may help confirm the diagnosis of hereditary ATTR amyloidosis in symptomatic cases, as it is noninvasive, easy to execute, and causes minimal discomfort to patients. Further studies focusing on amyloid deposits in minor salivary gland in FAP patients from both endemic and nonendemic areas should be conducted to reinforce the reliability and importance of this tool in the diagnosis and prognosis of familial polyneuropathies.

Compliance with ethical standards

Conflict of interest None declared.

References

- Planté-Bordeneuve V, Said G (2011) Familial amyloid polyneuropathy. *Lancet Neurol* 10:1086–1097
- Shin SC, Robinson-Papp J (2012) Amyloid neuropathies. *Mt Sinai J Med* 79:733–748
- Coelho T, Maurer MS, Suhr OB (2013) THAOS—The Transthyretin Amyloidosis Outcomes Survey: initial report on clinical manifestations in patients with hereditary and wild-type transthyretin amyloidosis. *Curr Med Res Opin* 29:63–76
- Saporta MA, Zaros C, Cruz MW et al (2009) Penetrance estimation of TTR familial amyloid polyneuropathy (type I) in Brazilian families. *Eur J Neurol* 16:337–341
- Hemminki K, Li X, Försti A, Sundquist J, Sundquist K (2013) Incidence of hereditary amyloidosis and autoinflammatory diseases in Sweden: endemic and imported diseases. *BMC Med Genet* 14:88
- Kato-Motozaki Y, Ono K, Shima K et al (2008) Epidemiology of familial amyloid polyneuropathy in Japan: identification of a novel endemic focus. *J Neurol Sci* 270:133–140
- Ando Y, Coelho T, Berk JL et al (2013) Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet J Rare Dis* 8:31
- Hund E (2012) Familial amyloidotic polyneuropathy: current and emerging treatment options for transthyretin-mediated amyloidosis. *Appl Clin Genet* 5:37–41
- Guy CD, Jones CK (2001) Abdominal fat pad aspiration biopsy for tissue confirmation of systemic amyloidosis: specificity, positive predictive value, and diagnostic pitfalls. *Diagn Cytopathol* 24:181–185
- Delgado WA, Mosqueda A (1989) A highly sensitive method for diagnosis of secondary amyloidosis by labial salivary gland biopsy. *J Oral Pathol Med* 18:310–314
- Hachulla E, Janin A, Flipo RM et al (1993) Labial salivary gland biopsy is a reliable test for the diagnosis of primary and secondary amyloidosis. A prospective clinical and immunohistologic study in 59 patients. *Arthritis Rheum* 36:691–697
- Dupond JL, de Wazières B, Saile R et al (1995) Systemic amyloidosis in the elderly: diagnostic value of the test of subcutaneous abdominal fat and the labial salivary glands. Prospective study in 100 aged patients. *Rev Med Intern* 16:314–317
- Lechapt-Zalcman E, Authier FJ, Creange A, Voisin MC, Gherardi RK (1999) Labial salivary gland biopsy for diagnosis of amyloid polyneuropathy. *Muscle Nerve* 22:105–107
- Dhingra S, Krishnani N, Kumari N, Pandey R (2007) Evaluation of abdominal fat pad aspiration cytology and grading for detection in systemic amyloidosis. *Acta Cytol* 51:860–864
- Do Amaral B, Coelho T, Sousa A, Guimarães A (2009) Usefulness of labial salivary gland biopsy in familial amyloid polyneuropathy Portuguese type. *Amyloid* 16:232–238
- Sacsaquispe SJ, Antúnez-de Mayolo EA, Vicetti R, Delgado WA (2011) Detection of AA-type amyloid protein in labial salivary glands. *Med Oral Patol Oral Cir Bucal* 16:e149–e152
- Mercan R, Bitik B, Tezcan ME et al (2014) Minimally invasive minor salivary gland biopsy for the diagnosis of amyloidosis in a rheumatology clinic. *ISRN Rheumatol* 2014:354648
- Adams D, Suhr OB, Hund E et al (2016) First European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy. *Curr Opin Neurol* 29(Suppl 1):S14–S26
- Coutinho P, da Martins Silva A, Lopes Lima J, Resende Barbosa A (1980) Forty years of experience with type I amyloid neuropathy. Review of 483 cases. In: Glenner G, Costa P, de Freitas A (eds) *Amyloid and amyloidosis*. Excerpta Medica, Amsterdam, pp 88–98
- Palácios SA, Bittencourt PL, Cançado EL et al (1999) Familial amyloidotic polyneuropathy type 1 in Brazil is associated with the transthyretin Val30Met variant. *Amyloid* 6:289–291
- Bittencourt PL, Couto CA, Clemente C et al (2005) Phenotypic expression of familial amyloid polyneuropathy in Brazil. *Eur J Neurol* 12:289–293
- Kollmer J, Hund E, Hornung B et al (2015) In vivo detection of nerve injury in familial amyloid polyneuropathy by magnetic resonance neurography. *Brain* 138:549–562