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DIAGNOSTIC DELAY IN AUTOIMMUNE ORAL DISEASES.

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ABSTRACT

Objectives: Autoimmune diseases affect about 5% of the general population, causing various systemic and/or topical clinical manifestations. The oral mucosa is often affected, sometimes as the only involved site. The misdiagnosis of oral autoimmune diseases is and underreported issue.

Methods: This narrative review focuses on diagnostic delay in oral autoimmune diseases (oral lichen planus, oral pemphigus vulgaris, mucous membrane pemphigoid, oral lupus erythematosus, orofacial granulomatosis, oral erythema multiforme and Sjogren syndrome). An extensive literature research was conducted via MEDLINE, Embase and Google Scholar databases for articles reporting the time spent to achieve the correct diagnosis of oral autoimmune diseases.

Results: Only 16 studies reported diagnostic delay in oral autoimmune diseases. Oral autoimmune vesiculobullous diseases are usually diagnosed after 8 months from the initial signs/symptoms, the Sjogren Syndrome diagnosis usually requires about 73 months. No data exist about the diagnostic delay in oral lichen planus, oral lupus erythematosus, orofacial granulomatosis, and oral erythema multiforme.

Conclusions: The diagnosis of oral autoimmune diseases can be difficult due to the non-specificity of their manifestations and the unawareness of dentists, physicians, and dental and medical specialists about these diseases. This can lead to a professional diagnostic delay and a consequential treatment delay. The delay can be attributed to the physicians or/and the healthcare system (Professional Delay) or the patient (Patient's Delay).

Keywords: diagnostic delay, oral autoimmune diseases, patient's delay, professional delay, vesciculo-bullous diseases

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1. AUTOIMMUNE DISEASES AND THEIR ORAL MANIFESTATIONS

Autoimmune diseases (ADs) comprise multiple chronic conditions defined by a dysregulation of the immune system cells, causing inflammation and tissue damage (Xiao et al., 2021). More than 80 different ADs are known, with a prevalence ranging from 5 to 500 per 100.000 (Cooper et al., 2003). According to the American Autoimmune Related Diseases Association (AARDA), ADs are frequently misdiagnosed due to the non-specificity of symptoms and the limited knowledge of physicians about ADs. AARDA reported an overall mean time of 5.6 years between the onset of the symptoms until the final diagnosis for the most common autoimmune pathologies (American Autoimmune Related Diseases Association, Inc., 2013). This delay also occurs when oral mucosa is affected, probably due to the variability of the clinical appearance of ADs oral lesions and their relatively low prevalence. Oral lesions may be the first sign of ADs, and their early identification and treatment may prevent the spread of the disease (Saccucci et al., 2018).

The most reported AD affecting the oral cavity is lichen planus (OLP), while oral pemphigus vulgaris (OPV), mucous membrane pemphigoid (MMP), systemic lupus erythematosus (SLE), orofacial- granulomatosis (OFG) and erythema multiforme (EM) are less common. Their incidence and prevalence rates vary depending on the applied diagnostic criteria (Saccucci et al., 2018). OPV and MMP are autoimmune autoantibodies-mediated blistering diseases affecting the mucosae, and they are both considered rare diseases due to their very low incidence in the general population (Petruzzi et al, 2012). SLE incidence ranges from 0.3 to 23.2 per 100.000 person-year, and it is higher in women (Gergianaki et al., 2018). OFGs are another group of ADs that cause recurrent or persistent orofacial swelling. The prevalence of OFGs is unknown (Miest et al., 2016). Sarcoidosis, Melkersson-Rosenthal Syndrome, Rosacea, and Crohn's disease are the most reported OFG.

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2. THE DIAGNOSTIC DELAY IN GENERAL: DEFINITION AND CLASSIFICATION

Chronic ADs have a long course and may worsen over time. It does not exist a shared definition of reasonable diagnostic time for oral ADs.

According to Guneri et al., the "diagnostic delay" (DD) is defined as the "time lapse between the appearance of the first sign or symptom of the disease to the definitive diagnosis" (Guneri et al., 2014). DD can be attributed to both the patient and the doctors.

The "Patient delay" (PtD) is defined as the delay caused by the patient, i.e., the time from the first detection of a sign/symptom to the first consultation with a health care professional (Guneri et al., 2014). Patients may postpone or avoid medical consultations due to socio-economic factors, educational and cultural levels, and altered perceptions of their conditions' severity (Allen et al., 2015).

The patients' personality and history influence the PtD, too: anxious people generally refer to healthcare specialists at early stages and/or mild symptoms, while careless and neglected patients present longer PtD (Gao et al., 2009).

Andersen et al. proposed a "general model of total patient delay", including five delay intervals before the treatment: the time before a person interprets a symptom as a sign of illness ("appraisal delay"), the time until deciding to seek professional medical care ("illness delay"), the time taken to act upon this decision ("behavioral delay"), the time needed to receive an appointment ("scheduling delay") and the time going from the first visit to the start of therapy ("treatment delay"), although this last one is not to include in the PtD according to other studies (Walter et al., 2012).

In some cases, the request for a consult may not come directly from the patients but from friends or relatives who convince them to refer them to special medical or dental facilities (Walter et al., 2012).

No statistically significant correlation emerged between PtD and civil status (Rogers et al., 2011). Some studies report longer PtD in men than women and elderly patients, especially if affected by dementia (Lauritano et al, 2019).

High socio-economic status can be related to greater attention to health and a higher frequency of medical consultations. On the contrary, patients with a low level of education may wait to seek medical advice due to unawareness of the diseases or for economic reasons (Gao et al, 2009). PtD is not only due to the patient's decisions but also related to the accessibility of the healthcare system and the costs of dental care. They identify a "system delay" consisting of the impediments and obstacles to access to healthcare services (Allen et al., 2015). The patient's residence can also affect the PtD: specialist care may not be available in rural areas, forcing the resident patients to cover long distances to obtain a diagnosis (Kerdpon et al., 2001). Villa et al. reported that patients with

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oral autoimmune lesions travelled longer distances (Villa et al., 2015).

Patients often wait for auto-resolution (Rogers et al., 2011), while, in other cases, they recur to over-the-counter medications or home remedies (Sawair et al., 2010).

Characteristics of signs and symptoms may influence PtD too. More severe pain or discomfort and wider and more visible lesions are more likely to be reported by the patients (Ministero della Salute (2015).

The symptoms investigated in oral cancer studies may not be valid for oral ADs: cancer causes symptoms only in advanced stages, while ADs generally cause burning and widespread pain since their onset.

One of the significant causes of PtD is patients' poor knowledge about oral pathologies; scientific societies are promoting information campaigns to increase awareness and spread the prevention of oral cancer (Allen et al., 2015).

"Professional delay" (PfD) is the time from the first examination by a health care provider to the definitive diagnosis (Allen et al., 2015). PfD is due to errors or defaults of health professionals who examined the patient before the specialist who performed the final diagnosis.

In figure 1, the several items building the diagnostic delay are illustrated.

Several studies reported how PfD relates to multiple medical consultations (Hassona et al., 2018; Daltaban et al 2020). This could be due to doctors referring patients to other professionals when unfamiliar with their conditions or to the patients searching for second opinions. Patients often start a "health pilgrimage" to several specialists, leading to increased health costs (Haberland et al., 1999).

In most cases, patients initially turn to dentists. As indicated by the American Dental Association Council on Scientific Affairs, dentists should perform a proper screening of the oral mucosa with a visual and tactile examination during each visit to detect potentially malignant and malignant lesions or any other pathologies (Rethman et al., 2012; Nicotera et al., 2004).

In case of mucosal lesions, dentists should remove possible causes and, if the lesion persists, perform a biopsy, or refer the patient to a secondary or tertiary care center (Villa et al., 2015).

Oral ADs, in many cases, are diagnosed only in case of skin or other organ involvement, when the patients tend to refer to other specialists, even though at this stage, the disease is generally already more severe (Daltaban et al., 2020).

Moreover, some cases require supplementary procedures to get a proper diagnosis, such as direct immunofluorescence or immunohistochemistry.

Oral ADs do not present typical features and are usually misdiagnosed with aphthous stomatitis, herpetic stomatitis, or candidiasis. This leads to prolonged inadequate therapies such as antibiotics,

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topical steroids, antifungals, and mouthwashes (Daltaban et al., 2020).

Dentists' PfD may be linked to difficulty in managing mucosal lesions due to inadequate university education, especially in some geographic areas (Ergun et al., 2009).

Allen and Farah highlighted how dentists do not feel the responsibility to screen oral mucosa (Allen et al., 2015). Moreover, the attitude toward managing oral mucosal diseases also depends on where they work (at private offices, dental clinics, or universities) and the tasks they perform (Ergun et al., 2009). Then, Oral Medicine is a recognized dentistry specialty only in some countries (Rogers et al., 2011).

Dental hygienists are also trained in oral cancer risk factors and often screen mucous membranes during oral hygiene procedures (Nicotera et al., 2004). Cooperation with hygienists helps ADs management, too (Scattarella et al., 2011).

Patients do not always refer to dentists for mouth health issues at first but to general practitioners, dermatologists, otolaryngologists, and maxillofacial surgeons (Daltaban et al. 2020), while other studies reported that patients refer equally to dentists and general practitioners (Bascones-Martínez et al., 2015). Patients with ADs often refer to dermatologists in the presence of skin lesions along with mouth-related symptoms (Hassona et al., 2018). Many patients believe that dentists only take care of teeth and gums and refer to general practitioners for oral mucosal lesions (Singh et al., 2006).

The specialists most frequently attended in case of oral symptoms are represented in figure 2.

Sarumathi et al. noted that most general practitioners performed a routine oral examination and showed moderate awareness of common oral diseases (Sarumathi et al., 2013), while Allen et al. showed that general dentists detected all the analyzed mucosal lesions, while general practitioners only a few cases (Allen et al., 2015).

Greater cooperation between dentists and other specialists may reduce PfD and facilitate the diagnostic pathway.

3. DIAGNOSTIC DELAY IN AUTOIMMUNE ORAL DISEASES

3.1 Diagnostic delay in Oral Lichen Planus

OLP is one of the more common autoimmune oral mucosal diseases, but there are few available data about DD in OLP. OLP lesions showing a reticular pattern are more likely to be recognized, while differential diagnosis is more challenging in atypical OLP forms (Idrees et al., 2020).

The erosive form is associated with pain, functional limitation, and discomfort, impacting oral health and quality of life. On the other hand, the absence of symptoms of white OLP forms may delay consultation. The clinical and histopathological characteristics of OLP must be differentiated from lichenoid dysplasia, lichenoid lesions, oral lupus, and chronic ulcerative stomatitis (Saccucci

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et al., 2018). Allen et al. found that PtD was the major component of the delay in OLP (Allen et al., 2015).

An early diagnosis and treatment of OLP can help to prevent the worsening of the disease symptoms and reduce the risk of a potential neoplastic transformation (American Autoimmune Related Diseases Association, Inc., 2013; Lauritano et al., 2016).

3.2 Diagnostic delay in Oral Pemphigus Vulgaris

Pemphigus Vulgaris is a chronic autoimmune disease that can affect the skin or/and mucosae (Petruzzi et al., 2021). Oral lesions are less recognizable than skin ones. When the oral cavity is the only site involved, patients report a long DD Villa et al., 2015). Various studies tried to quantify DD in OPV (Table 1). In 1977 Zegarelli et al. described 28 patients that initially showed OPV lesions with an average value of DD of 6.8 months (Zegarelli et al., 1977). Laskaris et al., in a sample of 157 patients (71.9% of which initially showed OPV lesions), reported a DD value of 1 year (Laskaris et al., 1982). Hassona et al. found a much lower average delay (5.9 to 7.8 months), distinguishing the two components of the delay and founding similar PtD and PfD values (Hassona et al., 2018).

Hassona et al. and Daltaban et al. showed no statistically significant correlation between the delay and demographic factors (Hassona et al., 2018, Daltaban et al., 2020).

Laskaris et al. correlated the delay with the lesion site, highlighting that OPV delay was double than of cutaneous PV (Zegarelli et al., 1977). Daltaban et al. showed that none of their patients had been diagnosed until the appearance of the skin lesions (Daltaban et al., 2020).

Hassona et al. and Daltaban et al. noticed that the DD was significantly longer (50 days) in patients who initially presented desquamative gingivitis than ulcers and erosions (Hassona et al., 2018; Daltaban et al., 2020). Daltaban et al. reported that patients with OPV mimicking aphthous stomatitis had a longer DD (Daltaban et al., 2020).

Hassona et al. showed a statistically significant negative correlation between PtD and symptoms severity score using Saraswat scoring system (Hassona et al., 2018).

Zegarelli et al. highlighted how most patients with OPV lesions consulted more dentists and physicians to reach the diagnosis (Zegarelli et al., 1977; Daltaban et al.) quantified an average of 6.27 consultations before the definitive diagnosis of PV. The number of consultations was doubled in patients with oral onset compared to patients with skin onset (Daltaban et al., 2020). Hassona et al. showed that PfD was significantly correlated with the number of previous consultations, which was averagely of 3.1 (Hassona et al., 2018).

The first healthcare professionals consulted were general medical practitioners and dentists, while

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the most consulted specialists were dermatologists, maxillofacial surgeons, and periodontists (Hassona et al. 2018). Patients consulted an average of 4.28 clinicians to obtain the diagnosis in case of exclusively oral lesions. Patients with skin lesions referred to half of the clinicians to obtain a diagnosis (Sirois, 2000).

Patients frequently receive a first diagnosis of "monilia, herpes, pharyngitis, etc." (Lauritano et al., 2016), and many patients are erroneously treated for an extended period for aphthous or herpetic stomatitis or candidiasis (Arduino et al., 2019).

Daltaban et al. found that 80% of OPV were misdiagnosed as aphthous stomatitis by general practitioners (Daltaban et al., 2020). Hassona et al. noted that PtD was longer when patients tried home remedies and over-the-counter medications before consulting a healthcare professional (Hassona et al, 2018).

3.3 Diagnostic delay in Mucous Membrane Pemphigoid

The first MMP sign is frequently a painful erythematous band along the gingiva followed by dryness, desquamation, and blisters (Petruzzi et al., 2012) It is often misdiagnosed as periodontitis or gingivitis and treated as such. In some cases, antiseptic and analgesic mouthwashes are prescribed (Vitali et al., 2002). Recognizing desquamative gingivitis during regularly performed periodontal practice could help decrease underdiagnosed cases of MMP (Ergun et al., 2009).

Delayed diagnosis and inappropriate treatment lead to the progression of the disease and the appearance of extra-oral lesions (Petruzzi et al., 2021). Ophthalmic involvement is considered a marker of severity and can lead to conjunctival scarring up to blindness (Vitali et al., 2002).

Untreated MMP shows an increase in symptoms over time with a severe worsening in quality of life and a mortality rate of 90% (Bascones-Martínez et al., 2015).

MMP's DD is usually lower than OPV (Petruzzi et al., 2021). Laskaris et al. found an average DD of 13.2 months in 55 MMP patients (Laskaris et al., 1982). A lower value of 5.5 months was found by Hassona et al. The mean value of PtD (2.8 months) was like the PfD one (2.6 months) (Hassona et al., 2018).

General dentists should carefully evaluate chronic gingival lesions and dental hygienists, suspect MMP diagnosis and address the patient to oral medicine specialists or tertiary care centers (Ergun et al., Scattarella et al., 2011).

Table 1 resumes the most relevant data about DD in OPV and MMP reported in Literature.

3.4 Diagnostic delay in Oral Lupus Erythematosus

Oral lesions often represent the first sign of the SLE and are often underdiagnosed since they are asymptomatic in more than half of the cases (Petri et al., 2012). Oral involvement of SLE can be

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misdiagnosed as leukoplakia or OLP when there are white streaks (Petri et al., 2012). Oral ulcers are the most common lesions related to SLE and are included in the Systemic Lupus International Collaborating Clinics (SLICC) primary clinical criteria classification. SLE usually is diagnosed only after cutaneous and renal manifestations (Petri et al., 2012).

There is a lack of studies about DD in oral SLE. Novak et al. found that half of the SLE patients had a median of 6 months DD (Novak et al., 2018). Cornet et al. found a median of 2 years DD in a sample of European patients: more than 30% had oral ulcers, and more than 50% had dry mouth or eyes (Cornet et al., 2020). SLE is often associated with SS presenting specific clinical and serologic features.

3.5 Diagnostic delay in Orofacial Granulomatosis

OFGs are an extremely heterogeneous group of pathologies characterized by a common histopathological aspect (Miest et al., 2016). The clinical history of patients is influenced by the course of the lesions and by the presence of other signs and symptoms specific to each different OFG, e.g. patients suffering from Melkersson-Rosenthal syndrome often present their symptoms spread out over a long time (Miest et al., 2016). Rarely, OFGs may initially cause gingival enlargement and may be misdiagnosed with gingival fibromatosis or hormone/drug-related gingival enlargement (Cornet et al., 2020).

Orofacial swellings may precede the development of other organs' involvement; dentists could be the first to detect these conditions playing a pivotal role in the multidisciplinary approach to their diagnosis (Bansal et al., 2015).

Studies about DD in OFGs are lacking, probably due to the low incidence and significant variability of the clinical manifestations of these patients. The available case reports show a DD of up to 16 years (Cornet et al., 2020).

3.6 Diagnostic delay in erythema multiforme

EM includes four immune-mediated mucocutaneous disorders: EM minor, EM major, Stevens-Johnson syndrome, and toxic epidermal necrolysis (Scully et al., 2008).

The oral mucosa can be involved together with the skin or be the only site affected in EM. The clinical appearance of oral EM ranges from bullous lesions to erosions to painful erythematous areas (Scully et al., 2008). The mild forms are generally self-limiting within weeks, even though "recurrent EM" may occur in some cases (Wetter et el., 2010). Other cases require pharmacological treatment with antiviral, immunosuppressants and/or steroids, while the more severe forms like toxic epidermal necrolysis need hospitalization.

Due to the variability of its clinical appearance and etiopathogenesis, EM is not always recognized.

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Moreover, no universally accepted diagnostic criteria exist, and to date, the diagnosis of this disease continues to be made by exclusion based on the patient's medical history (Celentano et al., 2015). Not always patient refers to dentists in case of mild form, mistaking EM lesions for aphthous stomatitis, and often the disease resolves itself before reaching a diagnosis; while the generalized forms are generally of medical internist's competence and require hospitalization.

Given that and the poor data present in Literature, it is difficult to assess the diagnostic delay in oral EM.

3.7 Diagnostic delay in Sjögren's syndrome

Diagnosing SS can be challenging, and the treatment delay worsens signs and symptoms (Wang et al., 2021). Data shows that more than half of SS patients are underdiagnosed (Wang et al., 2021). Primary SS is correctly diagnosed only in 33.3% of patients with dry eyes as an early symptom (Fox et al., 2005). Dryness of mouth and eye rarely induces patients to consult a specialist (Lin et al., 2010).

Often characteristic symptoms of SS only appear in late stages, making the diagnostic pathway difficult. Sometimes, there is an atypical presentation of SS, with joint and muscle pain, skin rashes, chronic dry cough, tingling, facial pain, neurological manifestations, vaginal dryness, and disabling fatigue. Moreover, SS symptoms may be shared with other conditions, such as atopic disease, anxiety, drug side effects, burning mouth syndrome, and menopause (Salerno et al., 2016). Sometimes physicians and dentists treat each symptom individually and do not further investigate systemic conditions. Due to initial oral or ocular involvement, patients often refer to ophthalmologists or dentists at first instance. According to American- European SS consensus guidelines, a multidisciplinary team approach is generally needed to diagnose and manage the disease (Vitali et al., 2002).

Several studies tried to quantify the delay associated with a diagnosis of SS with different results (Table 2). The highest delay value was 10 years, as reported by Manthorpe et al., who also noted that patients reached a diagnosis only after consulting "several doctors" (Manthorpe et al., 1997). A delay of about 6 years was also noticed by Skopouli et al. (Skoupuli et al., 2000) and Garcia-Carrasco et al. (García-Carrasco et al., 2002). The most significant sample of 573 SS patients was described by Lin et al. with an average DD of 48 months. They noted a significant DD reduction after 2002 (from 57 to 24 months) (Lin et al., 2010). Instead, Zhao et al. reported an increase in delay from an average of 51.6 months in 1997 to one of 144 months in 2015 (Zhao et al., 1997; Zhao et al., 2015). In 2012 the Sjögren's foundation assessed that the average diagnosis time of 6 years was too high and launched the "5-Years Breakthrough Goal" to reduce this value by 50%. In 2018 they announced that the delay value reached 2.8 years, the lowest recorded value (Sjögren's

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Foundation; 2018). Wang et al. reported a DD range between 2 to 6 years (Wang et al.,2021). Geographical factors were not reported to influence the DD (Lin et al., 20120; Zhao et al., 1997; Zhao et al., 2015).

4. CONCLUSIONS

The DD of oral ADs is still largely underestimated and poorly investigated. An early diagnosis and specific treatment may significantly improve the prognosis of the patients and the quality of their lives. Dentists should be able to recognize such lesions and should refer the patients to secondary or tertiary health care centers, thereby reducing PfD.

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TABLES CAPTION

Table 1. Reported data on diagnostic delay in Pemphigus and Pemphigoid diseases.
Table 2. Reported data on diagnostic delay in Sjogren's Syndrome

FIGURES CAPTION

Figure 1. Graphical representation of diagnostic delay in all its parts.
Figure 2. Graphical representation of most frequent oral symptoms, specialists attended and final reached diagnosis.

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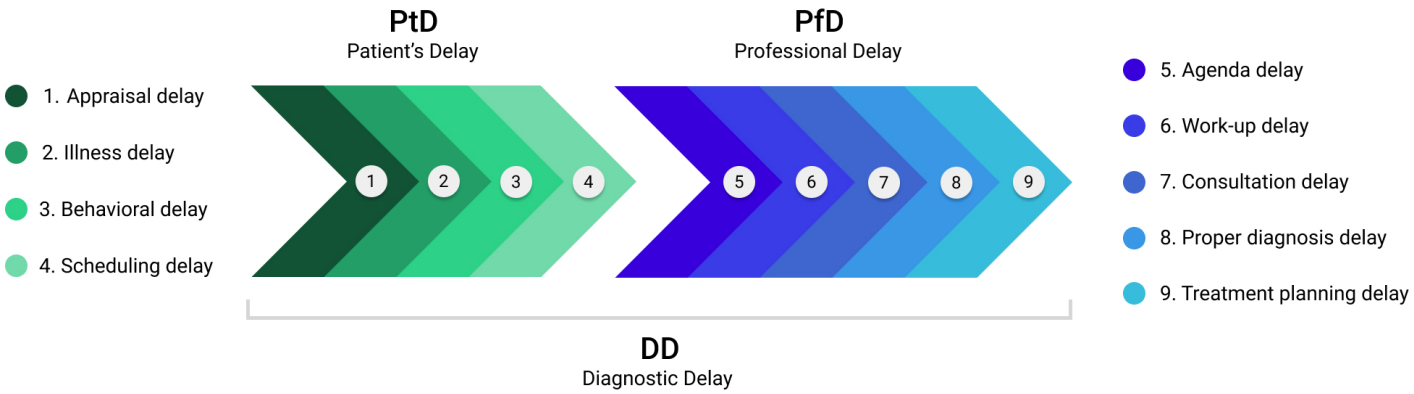

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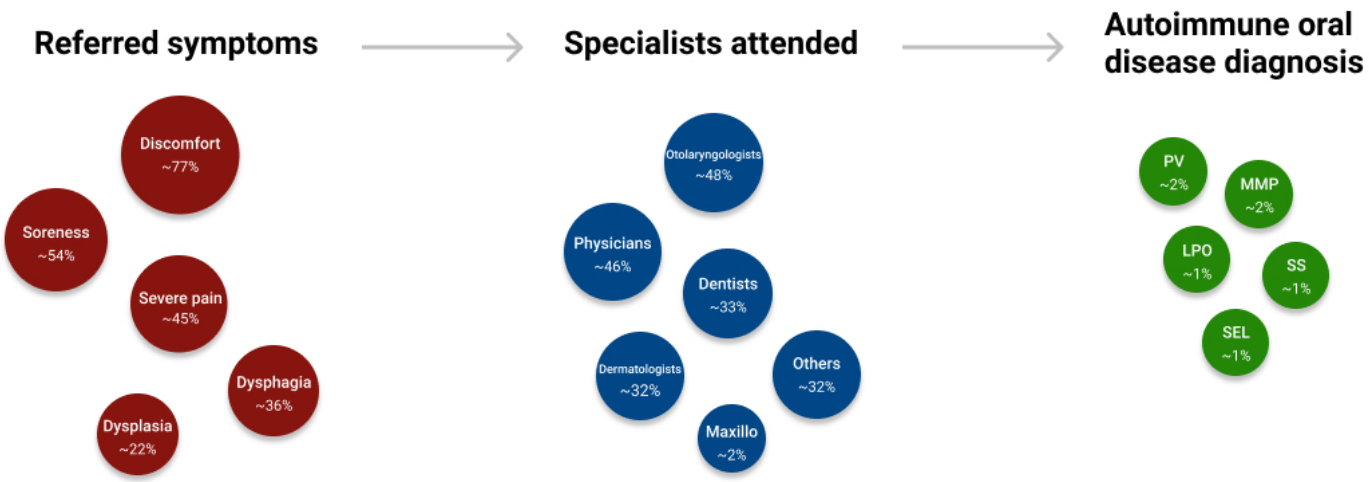

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Table 1: Reported data on diagnostic delay in Pemphigus and Pemphigoid diseases.

Author	Zegarelli et al. 1977	Laskaris et al. 1982		Scully et al. 1999	Sirois et al. 2000	Hassona et al. 2017	Arduino et al. 2019	Daltaban et al. 2020
Study design	Retrospective	Prospective		Retrospective	Retrospective	Prospective	Prospective	Prospective
N. patients	28	212		55	99	27	98	36
Oral AD	PV	PV	MMP	PV	PV	PV, PNP, MMP, LAD	PV	PV
Mean age (years)	52.8	54.4	66	50	54.3	52.6	54.6	42.8
M:F ratio	1:1.2	1:1.6	1:1.5	1:1.5	1:2.3	1:5.8	1:1.7	1:2.3
Initially oral involvement (%)	64	68.1	96.4	100	79.8	100	100	83.3
Oral affected sites (%)	24.5 tongue/floor 23.6 buccal mucosa 20.1 palate 19.1 gingivae 12.7 lips	26.7 palate 23.3 buccal mucosa 23.3 lips 17.8 tongue/floor 8.9 gingivae	34.3 gingivae 31.4 buccal mucosa 13.7 palate 8.8 alveolar ridge 7.9 tongue 3.9 lips	30.1 buccal mucosa 26.3 tongue/floor 18.6 palate 14.8 lips 10.2 gingivae	NA	27.8 buccal mucosa 26.6 palate 19.5 gingivae 14.7 tongue/floor 11.4 lips	32,9 buccal mucosa 22.8 palate 18.3 tongue/floor 17.5 gingiva 8.5 lips	30.4 tongue/floor 25.9 buccal mucosa 18.8 palate 14.2 gingivae 10.7 lips
Oral signs (%)	89.3 erosions/ulcers 10.7 desquamative gingivitis	NA	60 erosions/ulcers 40 desquamative gingivitis	90 erosions/ulcers 5 desquamative gingivitis 5 NA	NA	63 erosions/ulcers 37 desquamative gingivitis	100 erosions/ulcers	60 erosions/ulcers 27 desquamative gingivitis 13 aphthous-like lesions
Oral symptoms (%)	64.1 pain 35.9 dysphagia	91.4 mild discomfort 8.6 severe pain	94.3 mild discomfort 5.7 severe pain	100 pain/discomfort	59.9 pain 40.1 dysphagia	65.8 pain/discomfort 34.2 dysphagia	69.4 soreness 30.6 severe pain	44.5 pain/discomfort 33.3 dysphagia 22.2 dysphasia
N. consultations (mean)	NA	NA	NA	NA	4,28	3,1	NA	6.27 OMII 3.33 SII
First specialist attended (%)	NA	NA	NA	NA	53 physicians 47 dentists	51.9 other specialists 25.9 physicians 22.2 dentists	NA	59 physicians 29 dentists 12 other specialists
Empiric proposed treatments	antibiotics, antimycotics, bicarbonate rinses, silver nitrate, cough medicines, vitamins	NA	NA	NA	NA	antibiotics, analgesics, mouth washes, home remedies	NA	antibiotics, steroids, mouthwashes, antimycotics, vitamins, colchicine, antiviral agents, anxiolytics, antidepressants, periodontal treatment
Misdiagnoses	monilia, herpetic stomatitis, pharyngitis, gingivitis, diphtheria, necrotic gingivitis, menopause, geographic tongue, ulcerative stomatitis, tonsillitis	NA	NA	NA	NA	NA	aphthous stomatitis, herpetic stomatitis, oral candidiasis	aphthous stomatitis, oral candidiasis, Oral squamous cell carcinoma, infectious stomatitis, Behçet disease, plaque-induced gingivitis, anxiety/depression
Mean DD (months)	6.8	11.7 OMII 4.6 SII	13.2	6.75	7.29	5.9 (3.1 PtD+2.8 PfD)	6	6.73 OMII 3.50 SII

AD: Autoimmune diseases; **PV:** Pemphigus vulgaris**; MMP:** Mucous Membrane Pemphigoid; **PNP:** Paraneoplastic Pemphigus; **LAD:** Linear IgA Disease;
NA: Not Available; **OMII:** Oral Mucosa Initially Involved**; SII:** Skin Initially Involved**; DD:** Diagnostic Delay; **PtD:** Patient Delay; **PfD:** Professional Delay**.**

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Table 2: Reported data on diagnostic delay in Sjogren's Syndrome

Author	Manthorpe et al. 1996	Zhao et al. 1997	Skopouli et al. 2000	Garcia-Carrasco et al. 2002	Lin et al. 2010	Sjogren's foundation 2012	Jonsson et al. 2013	Zhao et al. 2015	Sjogren's foundation 2018
Country	Denmark	China	Greece	Spain	China	USA	Sweden	China	USA
N. patients	NA	116	261	400	573	NA	44	483	NA
Mean age at the onset (years)	NA	38,4	NA	52,7	39	NA	53	41,7	NA
M:F ratio	NA	1:7.3	1:25.1	1:13.8	1:10.7	NA	1:13.7	1:17	NA
Mean DD (months)	120	51.6	72	74.9	48	72	44.4	144	33.6

NA: Not Available; **DD:** Diagnostic Delay. **Total mean DD**: 73 months.

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