Editorial

Outcome measure in childhood Sjögren's disease: where do we stand?

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Received on December 16, 2023; accepted in revised form on February 19, 2024.

Clin Exp Rheumatol 2024; 42: 2344-2345.

Key words: Sjögren's disease, paediatric Sjögren's disease, ESSDAI, ESSPRI

Competing interests: none declared.

Primary Sjögren's disease (pSD) is a slowly progressive autoimmune disease that predominantly affects the exocrine glands, primarily the salivary and lacrimal glands, resulting in the typical sicca symptom complex of dry eyes and dry mouth (1). However, extraglandular involvement can manifest in several potentially life-threatening ways, including neurological, renal, haematological, pulmonary, and vascular manifestations (1). SD can occur at any age, typically affecting women between 30 and 60 years. However, childhood onset is a rare entity, estimated to occur in around 1% of all patients (1, 2). In recent years, increasing knowledge has been gained about the clinical phenotype of paediatric SD (pedSD), highlighting the differences from the adult-onset disease and the need for different evaluation tools (2-6).

In pedSD patients, recurrent parotitis emerges as a primary feature during presentation and stands as the most common reason for referral to a paediatric rheumatologist (6, 7). Conversely, sicca symptoms are less frequently reported in paediatric SD compared to adult pSD. A systematic literature review of 198 pedSD patients revealed parotitis as the predominant symptom, observed in two-thirds of the patients in the cohort (6). In an international multicentre study enrolling 300 pedSD, almost half of patients presented recurrent or persistent parotitis, while only 35% exhibited both dry mouth and dry eyes. Within the same cohort, only 23% met ACR/EULAR classification criteria for SD (2). These results emphasise the issue of the current ACR/EULAR criteria, which are designed for research rather than diagnosis and have shown high sensitivity (>95%) in diagnosing adult SD (8, 9). However, when applied to pedSD, these criteria exhibit several limitations, relying on clinical elements expressing damage rather than disease activity (2, 4, 10). Xerostomia and xerophthalmia, entry criteria for classifying SD, are secondary to a well-established and overall long-standing gland damage and therefore may not be present in childhood (3, 11). Indeed, only 33% of childhood SD presented signs of ocular or salivary gland dysfunction (2). Furthermore, examinations to assess glandular dysfunction (such as the Schirmer test and unstimulated whole saliva) or inflammation (*i.e.* gland biopsy) are not routinely performed in all paediatric patients, likely due to the difficulty in performing them at this age and the lack of age-normal values (2). Even when performed in presence of sicca symptoms, these examinations are not associated with objective glandular involvement or a positive biopsy result (4).

On the contrary, systemic features such as fever, involuntary weight loss, or night sweats are more frequently reported in children with pedSD, often accompanied by extra-glandular manifestations such as cytopenias, vasculitis, or diffuse lymphadenopathies (2, 12). The systemic involvement in pedSD is further underscored by the high prevalence of positive antibody findings in these patients, with over 90% testing positive for antinuclear antibodies (ANA+), over 75% for Ro/SSA antibodies (Ro/SSA+), over 60% for rheumatoid factor (RF+), and over 50% exhibiting hypergammaglobulinemia. The antibody profile observed in pedSD closely mirrors that of young adults with pSD, indicating a cohort of patients characterised by high disease activity and a high incidence of signs of B-cell activation (13). To overcome this issue, child-specific criteria have been proposed (3, 14). However, their efficiency seems limited, achieving a sensitivity of 55% (2). Outcome measures have been validat-

ed in adult SD to assess disease activity (15). The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) score has been developed to evaluate the systemic disease activity across 12 activity domains (15). Paediatric SD present a higher ESSDAI score compared to adult SD because of a prominent systemic clinical phenotype characterised by an increased frequency of constitutional symptoms, lymphadenopathy, and cutaneous manifestations (5, 16). However, again, ESSDAI score has not yet been validated in children with SD. The only available investigation specifically addressing the use of ESSDAI in pedSD was a retrospective study conducted within a small-size cohort (16). The authors established a correlation between the use of systemic corticosteroids or immunosuppressant and an elevated ESSDAI score. However, this study could not assess changes in ESSDAI after treatment (16). The EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), a subjective tool developed to measure clinical disease activity, may also be used in pSD (15). This score includes three main self-reported indicators of disease activity: dryness, fatigue, and pain. Although ESSPRI is commonly used to evaluate the patient's symptoms in adult pSD, its correlation with objective parameters of glandular function is not well-established and conflicting (17, 18). SD is a remarkably heterogeneous disease and cluster characterisation in adult SD revealed that a higher ESSPRI score is associated with a sicca phenotype, higher levels of depression, a high prevalence of fibromyalgia and impaired QoL, despite a relative low frequency of systemic features, and high prevalence of fibromyalgia (18).

These limitations become more apparent in pedSD where fatigue and pain are rare manifestations, and sicca symptoms may be absent.

In conclusion, there is a need for age-specific diagnostic criteria and outcome measures for pedSD. Active involvement of pedSD patients is required to develop patient-reported outcomes specifically designed for this group of patients. These measures should enable the early interception of the disease before organ damage occurs and feasibly assess disease activity and response to therapy. An international collaborative effort is urgently required, as severe disease-modifying agents are currently under evaluation for adult patients, and the lack of reliable outcome measures in the paediatric age group might become a major limitation to clinical trials in this population.

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