Impairment of salivary function in juvenile idiopathic oligoarticular arthritis is a sign of early onset disease

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Abstract

Aim Recent evidences of the presence of reduced stimulated salivary flow rate and altered saliva composition in oligoarticular juvenile idiopathic arthritis (o-JIA) suggest a specific damage to the salivary glands. The aim of this cross-sectional study was to investigate whether reduced salivary flow rate could be related to age and gender at disease onset in o-JIA.

Methods A total of 57 Caucasian patients (41 females and 16 males) aged 5 to 16 years affected by o-JIA were consecutively enrolled in the study. Information on medication intake, dietary and oral hygiene habits were gathered through a standardised questionnaire. All patients underwent oral and sialometry examination.

Results Alteration in the stimulated salivary flow rate (SFR) was detected in 29 children; 18 and 11 of them displayed SFR < 3.5 ml and SFR between 3.5 and 5 ml, respectively, while 28 showed a normal SFR. Early disease onset ($p < 0.001$) and female gender ($p = 0.044$) were associated with very low SFR pattern. The rate of reduction in SFR decreased as age increased. For children less than 7 years old, the odds of suffering of very low SFR was 25-fold higher as compared to older JIA children (OR 24.94, 95% IC: 5.03, 123.77; $p < 0.001$).

Conclusion Early onset disease would seem to be associated with salivary glands impairment. Regular dental and salivary gland function assessments may be highly recommended in o-JIA patients considering that saliva collection is a non-invasive and inexpensive procedure.

KEYWORDS Autoimmune diseases; Juvenile idiopathic arthritis; Risk factor; Salivary glands; Xerostomia.

Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in childhood and represents a heterogeneous group of disorders characterised by chronic synovitis, arthralgia, and impaired joint mobility that begin before the age of 16 years and persist for more than 6 weeks [Barut et al., 2017]. JIA diagnosis depends on the clinical picture, rather than on laboratory tests, with other defined diagnosis being excluded. This may result in a diagnostic delay, which is a crucial obstacle for the introduction of proper treatment. The aetiology of JIA remains elusive. JIA is an autoimmune disease with a female predominance and it is likely that combinations of genes give rise to risk for different manifestations of JIA [Barut et al., 2017; Zuber, 2019]. The oligoarticular and polyarticular subtypes are the most common forms occurring in about 90% of cases [Macaubas et al., 2009; Zuber, 2019]. Due to differences in genetic and immunological features, it is likely that these two subtypes arise through distinct aetiopathogenetic pathways [Macaubas et al., 2009]. There is also emerging evidence that they represent heterogeneous entities suggesting the need for biologically-based refinement of childhood arthritis classification [Martini et al., 2019; Rezaei et al., 2020]. In this context, recent evidences identify salivary gland function impairment as a distinctive trait of a subset of children with JIA: many oligoarticular JIA (o-JIA) patients show a major increase in antioxidant enzyme activity suggesting a specific damage to the salivary glands [Brik et al., 2006; de Oliveira et al., 2016; Kobus et al., 2017]. Stimulated salivary flow rate (SFR) is mainly reduced in o-JIA compared to polyarticular JIA patients and could be considered a risk indicator for such subtype [Defabianis et al., 2021].

It is possible that the severity of salivary involvement may be related to the age at which o-JIA develops. It has been suggested that pathological mechanisms may differ according to the age of onset, being gene expression patterns and antibody repertoire different between children with early-onset and late-onset JIA disease [Barnes et al., 2010]. Indeed, patients with early-onset JIA display a B cell signature, have a different Ig κ light chain repertoire, and are predominantly antinuclear antibody (ANA) positive [Barnes et al., 2010; Nigrovic et al., 2018]. Interestingly, in adults suffering from rheumatoid arthritis the autoimmune changes affecting salivary glands are attributable to lymphocytic infiltration, which leads to cellular destruction, acinar atrophy and fibrosis [Janin-Mercier et al., 1982]. It has been postulated that, although human salivary glands develop already in prenatal life, their further functional development continues in childhood and ends in adolescence [de Paula et al., 2017]. Salivary glands function is regulated by the sympathetic and parasympathetic innervation [Pedersen et al., 2018]. Resting rate of salivary secretion gradually reduces in children up to the age of five - period during which the maturation of the nervous system takes place - confirming the progressive increase in inhibitory

signals from higher centres. In healthy children SFR was found to increase up to 15 years, while the role of the gender is less clear [de Paula et al., 2017; Söderling et al., 1993]. This may suggest a higher vulnerability of salivary glands in younger age. The aim of this cross-sectional study was to explore whether reduced salivary flow rate could be related to age and gender in o-JIA patients. Since pathologic mechanisms may vary with age understanding these processes may help in early detection of high-risk patients.

Methods

Study design and participants

All Caucasian children aged up to 16 years presenting to the Section of Paediatric Dentistry, C.I.R. Dental School, University of Turin between February 2019 and April 2021 with a diagnosis of o-JIA according to the International League of Associations for Rheumatology (ILAR) criteria were eligible to participate [Petty et al., 2004]. The differences between age in which symptoms attributable to JIA began, referred as age at onset, and age at the dental visit should not exceed 8–10 months.

Exclusion criteria included subjects who refused the saliva sampling and patients affected by medical conditions potentially impairing the salivary flow rate (diabetes mellitus, human immunodeficiency virus infection, history of radiotherapy, chemotherapy, or ongoing steroid treatment). Informed consent was obtained from parents/guardians of all participants included in the investigation. The study protocol was approved by the local ethics committee and was performed according to the ethical principles of the Helsinki Declaration.

Data collection

Data on medication intake, dietary habits and toothbrushing frequency were collected using a standardised self-reported questionnaire. A single specialist in paediatric dentistry recorded the level of oral hygiene (full-mouth plaque score [FMPS]) and the presence of any carious lesion or erosion on all erupted teeth based on the criteria established by the World Health Organization. Whole saliva sampling was conducted between 9.00 and 11.00 a.m., at least 2 hours after the consumption of any food or drink. SFR and salivary buffering capacity (SBC) of the stimulated saliva were measured using an in vitro test (Saliva-Check Buffer, GC) according to the manufacturer's instructions. Participants were asked to chew paraffin tablets for 5 min and expectorate saliva into a measuring cup over a period of 5 min. SFR was scored on a scale from 1 to 3, where 1 represented normal (> 5 ml), 2 low (between 5 and 3.5 ml) and 3 very low (< 3.5 ml) flow rate. A sample of the collected saliva was added to a kit test tube, and the resultant colour was compared with the colour chart. Very low SBC was 0 to 5, low was 6 to 9 and normal was 10 to 12. Finally, the acidity (pH) of the saliva was measured using pH test strips placed into the resting saliva for 10 seconds: pH was considered normal when between 6.8 and 7.8, moderately acidic when between 6 and 6.7 and highly acidic when between 5 and 5.9.

Statistical analysis

Statistical analysis was performed using SPSS software (IBM, Chicago IL, version 24.00). The study population was stratified into 3 groups based on SFR scores. Quantitative variables were shown as median and interquartile range when they did not achieve normality or as mean ± standard deviation when normally distributed. Qualitative variables were described as frequency. Inter-group differences were assessed using parametric (one-way analysis of variance) or non-parametric tests (Kruskal-Wallis test), followed by post-hoc tests for quantitative outcomes and $\chi 2$ test or Fisher exact test for categorical outcomes. Possible associations between salivary and clinical variables were examined by Spearman correlation analysis.

Multiple logistic regression analysis was performed to identify the independent predictive factors for SFR < 3.5 ml. Estimates were shown as odds ratio (OR) and 95% confidence interval (CI). A power analysis indicated that the sample size would be sufficient to demonstrate statistical significance at the $P < 0.05$ level with a power of 94%. The significance level was set at 5%.

Results

Study participants

A total of 57 Caucasian patients, 41 females and 16 males, ranging in age from 5 to 16 years (mean 10.1 ± 3.8 years) were serially recruited into this cross-sectional study. All participants were RF and human leucocyte antigen B27 (HLA-B27) negative; 9 of them (15.8%) had the extended subtype and 7 (12.3%) were ANA-negative. At the time of enrolment into the study no patient was taking DMARDs or biologic drugs. None complained of signs or symptoms related to Sjögren's syndrome, including mouth or eye dryness, and none was tested for extractable nuclear antigens (ENA) antibodies (SSA/Ro or SSB/La).

Clinical outcomes

Alterations in the SFR was detected in 29 children, of whom 18 and 11, respectively, displayed SFR < 3.5 ml and SFR between 3.5 and 5 ml, while 28 showed a normal SFR.

As shown in Table 1, statistically significant differences were observed in mean age and gender distribution among the three SFR patterns. Early onset ($p < 0.001$) and female gender ($p = 0.044$) were associated with very low SFR pattern with 77.8% of the affected children below 7 years of age. Neither ANA status nor dietary habits could be found to be of significant importance to SFR. Oral characteristics are summarised in Table 2. No statistically significant differences were observed in oral hygiene, caries experience and dietary habits among the SFR groups. Dental erosions were found in only 2 patients who exhibited very low SFR. SBC and pH value were found dependent on SFR. Median pH was significantly lower in very low SFR group in comparison to the other two groups ($p = 0.026$ and $p = 0.001$, respectively), while median SBC was lower in very low SFR as compared with normal SFR group ($p = 0.007$). A significant correlation was observed between SFR and both pH ($\rho = 0.471$, $p < 0.001$) and SBC ($\rho = 0.386$, $p = 0.003$).

The multiple logistic regression model confirmed the significant effects of age and gender on the occurrence of SFR < 3.5 ml. Female gender exhibited a 9-fold higher likelihood of suffering very low SFR as compared with male gender (OR 9.29, 95% IC: 1.27, 68.11; $p = 0.028$), and each one-year increase in age decreased by 0.46-fold the odds for having severe salivary gland function impairment (OR 0.46, 95% IC: 0.29, 0.72; $p = 0.001$). Under the age of 7 years, the odds of suffering of very low SFR was 25-fold higher as compared to older JIA children (OR 24.94, 95% IC: 5.03, 123.77; $p < 0.001$).

Discussion

There is increasing evidence of significant heterogeneity within

Parameter	SFR < 3.5 ml (n = 18)	SFR 3.5 to 5 ml (n = 11)	SFR > 5 ml (n = 28)	Total (n = 57)	*P*-value
Age, mean (S.D.) (years)	6.6 (1.5)	9.4 (3.0)	12.6 (3.2)	10.1 (3.8)	< 0.001
Age category, n (%)					< 0.001
5 – 7 years	14 (66.7)	5 (23.8)	2 (9.5)	21 (36.8)	< 0.001
8 – 12 years	4 (22.2)	4 (22.2)	10 (55.6)	14 (31.6)	
13 – 16 years	0	2 (11.1)	16 (88.9)	18 (31.6)	
Sex, male/female	2/16	6/5	8/20	16/41	0.044
Sweet or sweetened drinks daily intake, n (%)					0.743
< 3 times a day	7 (35.0)	4 (20.0)	9 (45.0)	20 (35.1)	
3 times a day	7 (24.1)	6 (20.7)	16 (55.2)	29 (50.9)	
> 3 times a day	4 (50.0)	1 (12.5)	3 (37.5)	8 (14.0)	
Acid diet, n (%)			-		0.373
No	13 (30.2)	11 (25.6)	19 (44.2)	43 (75.4)	
Moderate	3 (33.3)	0	6 (66.7)	9 (15.8)	
Severe	2 (40.0)	0	3 (60.0)	5 (8.8)	

S.D., standard deviation; SFR, stimulated salivary flow rate.

TABLE 1 Sociodemographic and lifestyle characteristics of the oligoarticular JIA subjects according to the SFR pattern.

Parameter	SFR < 3.5 ml (n = 18)	SFR 3.5 to 5 ml (n = 11)	SFR > 5 ml (n = 28)	Total (n = 57)	P-value
Toothbrushing frequency, n (%)					0.370
Once a day	6 (37.5)	5 (31.3)	5 (31.3)	16 (28.1)	
Twice a day	9 (26.5)	5 (14.7)	20 (58.8)	34 (59.6)	
> 2 times a day	3 (42.9)	1 (14.3)	3 (42.9)	7 (12.3)	
FMPS, mean (S.D.), %	52.2(12.1)	38.6 (18.1)	43.6 (19.2)	45.3 (17.5)	0.093
Buffering Capacity, median (IQR)	8.00 (7.8-10.0)	9.00 (9.0-11.0)	10.0 (9.0-11.0)	9.00 (8.0-10.0)	0.008
pH, median (IQR)	6.7 (6.4 – 7.2)	7.3 (6.8-7.6)	7.4 (7.2 -7.6)	7.2 (6.7-7.5)	0.001
Presence of at least one carious lesion, n (%)	8 (40.0)	5 (25.0)	7 (35.0)	20 (35.1)	0.292
Presence of at least one dental erosion, n (%)	2 (100)	0	0	2 (3.5)	0.130

IQR, interquartile range; JIA, juvenile idiopathic arthritis; FMPS, full-mouth plaque score; S.D., standard deviation; SFR, stimulated salivary flow rate

TABLE 2 Oral hygiene, salivary function and dental status of the oligoarticular JIA subjects according to the SFR pattern.

different JIA subtypes as well as of communalities among them, which are not accounted for in the actual ILAR classification system [Martini et al., 2019; Rezaei et al., 2020; Thompson et al., 2010]. One clinical parameter reported with biological implications is the age at onset, which looks like being more relevant than the number of the joints affected [Martini et al., 2019]. Differential gene expression patterns were found between patients with early- and late-onset JIA, regardless of the classification of oligoarticular or polyarticular JIA [Barnes et al., 2010].

The present study suggests a possible relationship between salivary glands involvement, disease onset before 7 years of age ($p < 0.001$) and female gender ($p = 0.044$) regardless of either ANA status or dietary habits. Early onset and female gender were associated with very low SFR pattern with 77.8% of the affected children younger than 7 years of age. Under the age of 7 years, the odds of suffering of very low SFR was 25-fold higher as compared to older JIA children. Thus, the co-existence of these factors could be predictive of o-JIA. At the same time a statistically significant positive association was observed between SFR, pH and SBC [Gao et al., 2016]. Nonetheless, oral hygiene and caries experience were comparable among the different SFR groups (Table 2) in contrast to previous studies reporting an association between poor salivary parameters and clinical variables [González-Abbate et al., 2014; Pyati et al., 2018]. JIA has been recognised to exert a negative impact on diet through poor intake (secondary to anorexia with active disease), difficulty chewing (TMJ disease) or sore mouth due to medications. The involvement of the upper limb can cause considerable functional disability and patients may have increased difficulty in performing oral hygiene procedures [Walton et al., 2000]. Furthermore, due to TMJ involvement, mouth opening may be painful and restricted, which may also impede efficient plaque removal [Pawlaczyk-Kamieńska et al., 2020]. Another aspect to be considered is the long-term use of sugar-based liquid medicines as alternatives to tablets in younger children to increase palatability and patient acceptance. These medicines have an high content in sugar (10–80%) and may be given up to four times per day, with a consequently large sugar intake increasing so the risk of dental caries [Severino et al., 2021]. The effect may be greater if they are taken at night or at bedtime when the protective buffering and cleansing effects of saliva are reduced as the SFR falls [Maguire and Rugg-Gunn, 1994]. Moreover, there is some evidence that children are often consoled with sweets from well-meaning parents and grandparents. The different results of our sample concerning oral hygiene and caries experience are probably due to the fact that the small number of patients examined are motivated to all aspects regarding dietary and oral hygiene practices, as well as parents and caregivers [Bello et al., 2020; Colombo et al., 2019] [Carli et al., 2021]. They had easy access to dental care and were strictly monitored [Cianetti et al., 2017]. [Giuca et al., 2021]. Currently, salivary diagnosis is drawing increasing attention as it is non-invasive, easy to collect, and exhibits greater patient compliance compared with other

methods. For many years we hoped that saliva could provide an alternative to blood for diagnosing systemic diseases, but this would be possible only if the blood constituents were transferred through the glandular epithelium in proportion to their blood concentration. This only applies to urea, glucose and free steroid hormones: in sialoadenitis, on the other hand, concentrations of sodium and chloride in the secretions of the affected glands increase, suggesting that inflammation mainly affects the duct system [Proctor and Shalaan, 2021]. This hypothesis is reinforced by the fact that the concentration of phosphate is generally decreased like in the Sjogren's syndrome [Kalk et al., 2001]. Generalised immune reactions may affect salivary glands by reducing the rate of secretion and thus increasing sodium and chloride concentrations. The endocrine disorders affecting salivary glands are those of the adrenal cortex. Aldosterone increases sodium absorption in the striated ducts of the salivary glands, reducing thereby sodium but increasing potassium concentration in saliva [Heintze and Dymling, 1985]. Indeed, salivary sodium-potassium ratio may be indicative of normal, excess or deficient secretion of aldosterone. This is consistent with data from a previous report describing significantly lower salivary concentration of potassium, but increased levels of sodium in JIA patients compared to healthy controls; furthermore, SFR was reduced in young JIA children [Siamopolou et al. 1989].

Conclusions

The findings of our study should be interpreted within the limitations of the cross-sectional study design and the small sample size and may be not generalisable to other populations. We can only speculate that SFR reduction may result from damage to the salivary glands due to the pro-inflammatory mediators involved in o-JIA pathogenesis [Barut et al., 2017]. The earlier is the onset of the inflammatory response in the secretory structures, perhaps more sensitive than joints to the disease, the more severe the course of the disease may be during growth. The results of our investigation are consistent with the view that age at onset may be an important characteristic for classification of certain JIA subtypes; pathologic mechanisms may differ in patients with early-onset and late-onset disease, with important implications for treatment.

For all these reasons, the role of paediatric dentistry in the multidisciplinary management of JIA is strategic: regular dental consultations and routine salivary gland function assessment may be recommended considering that saliva collection is a non-invasive, low-cost and simple procedure to perform. This is even more relevant in young children whose compliance is very low and are at risk to develop more severe form of disease. Due to the subtle damaging mechanisms of JIA, early diagnosis may be a major factor contributing in reducing long-term disability: the earlier a therapeutic strategy is established, the better results will be. More clinical evidences are needed to clarify these findings.

Conflict of interest

The authors declare the absence of any potential conflict of interests.

Competing interest

The authors declare that they have no competing interests.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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