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Investigation of Immune Alterations and Autoimmune Disorders in Juvenile Recurrent Parotitis: A Retrospective Study and Proposed Algorithm

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ABSTRACT

Introduction: Juvenile recurrent parotitis (JRP) is a rare, recurrent inflammation of the parotid glands occurring in children. The etiology remains unknown, and although the treatment is still debated, it is mainly symptomatic. There are currently no guidelines regarding the management of JRP. This study presents a consecutive series of cases where immune alterations and associated autoimmune disorders are investigated, proposing a study algorithm.

Methods: A retrospective study was conducted on patients diagnosed with JRP between January 2010 and July 2020. After clinical and ultrasound diagnosis, complementary examinations were performed to investigate associated immune, autoimmune, or infectious diseases.

Results: Twenty-five patients met the inclusion criteria and underwent investigation. The age at onset ranged from 18 months to 11 years, with a male predominance (68%). In most cases, the parotitis was unilateral (84%), with edema (100%), pain (68%) and fever (12%) being the main associated symptoms, averaging two episodes per year.

During additional evaluation, the autoantibody profile was positive in one patient, and antibody deficiency was found in two patients. Sialography was performed only in one patient, suggesting canalary dyskinesia. Additionally, one patient presented with sialolithiasis of the submandibular gland. Ultrasound was performed after the acute episode in 76% of the patients, revealing chronic changes in almost half of the cases. The potential cause of JRP was not identified in about one-third of the patients, and three children are still under investigation.

Discussion: The clinical course of JPR is generally self-limiting and resolves spontaneously after puberty. However, at diagnosis, all children should be screened to exclude immunodeficiency, Sjögren's syndrome and lymphoma.

Keywords: Juvenile recurrent parotitis; etiology; investigation; algorithm

INTRODUCTION

Juvenile recurrent parotitis (JRP) stands as a perplexing inflammatory condition affecting the parotid glands, predominantly observed in pediatric populations. It is a rare recurrent inflammation of the parotid gland[1-3], usually associated with non-obstructive and non-suppurative sialectasia of the parotid gland[1,4-10]. Characterized by recurrent episodes of parotid gland swelling, often accompanied by pain and fever, JRP poses diagnostic challenges and management dilemmas to healthcare providers worldwide. Other symptoms are malaise, redness, mild trismos, overlying erythema, and absence of lymph node involvement[4-9,11-15]. JRP is mostly unilateral, but it can have bilateral parotid inflammation, usually with a more predominant side[1,2,7,8,16,17].

Despite its prevalence as the second most common inflammatory gland disease of childhood, surpassed only by mumps prior to widespread vaccination[4,9,12,17]. The juvenile form of parotitis is reportedly ten times less common than the adult form[9]. JRP etiology remains elusive, with proposed mechanisms ranging from congenital ductal malformations to immunological dysregulation[18], indicating a predominantly idiopathic and likely multifactorial nature of this pathology[1,4-8,16,19]. Many theories advocate decreased salivary production with insufficient salivar outflow due to the combination of congenital ductal malformations and retrograde infections from the oral cavity. Other studies associate JRP with immunodeficiency, autoimmune diseases or allergies[1,2,4-8,11,13,16,17]. Dental malocclusion and poor oral hygiene can serve as predisposing factors[2,17]. The clinical course of JRP typically manifests as intermittent parotid gland swelling episodes, which may fluctuate in frequency and severity over time[1,20].

While many cases demonstrate a self-limiting nature, a subset of patients experiences persistent symptoms or recurrent episodes into adolescence and adulthood[1,4,6-9]. In 10-20% of cases JRP may persist[11], leading to chronic salivary dysfunction with severe sequelae[17]. These fluctuations in disease activity underscore the heterogeneity of JRP and the necessity for tailored diagnostic and therapeutic approaches.

Diagnostic evaluation of JRP relies on a combination of clinical criteria, imaging studies, and laboratory investigations to confirm the diagnosis, rule out alternative etiologies, and assess disease severity[4,6,8,13,17]. Laboratory investigation is usually carried out outside the acute phase, especially in the presence of one of the following factors: a child older than six years, bilateral inflammation of the parotid, suspicion of underlying chronic disease, or very frequent and severe episodes[7]. However, it can be useful in the acute phase if any complications are suspected (cellulitis, abscess, neoplasm)[7]. The investigation should include a complete blood count, C-reactive protein, erythrocyte sedimentation rate, quantification of immunoglobulins (Ig) (IgA, IgM, IgG and IgE), an autoimmunity study (antiendomysal antibodies, anti-transglutaminase antibodies, rheumatoid factor, anti-Ro/SSA and anti-La/SSB), viral serologies [Epstein-Barr Virus (EBV), Cytomegalovirus Infection (CMV), Human Immunodeficiency Virus (HIV), enterovirus, Mycoplasma, herpes and parotitis][7,12,13]. Ultrasonography and sialography are the most important complementary diagnostic tests, emerging as valuable tools for visualizing parotid gland morphology and detecting associated complications, providing essential guidance for clinical decision-making[6,8,9,21,22]. However, only sialography can detect changes in Stensen´s duct, such as a dotted appearance, delayed evacuation of the contrast médium and the severity of any inflammation[3,15]. Some studies also describe the use of magnetic resonance (MR), MR-sialography, computed tomography (CT) and CT-sialography for the diagnosis of JRP. Sialoendoscopy, a minimally invasive intervention serving both diagnostic and therapeutic purposes, has been recently applied and seems to be useful[4,6,17].

Management strategies for JRP primarily aim to alleviate symptoms, prevent glandular parenchymal damage, and improve patients' quality of life. Symptomatic relief through anti-inflammatory medications and adjunctive therapies is primary[1,8], while the role of antibiotics and immunomodulatory agents in managing complications requires further exploratios[14]. Initially, conservative treatment is favored, emphasizing warm compresses, massage of the parotid gland, oral hygiene, and fluid intake[1,6-8,14], with antibiotics reserved for bacterial co-infections or prophylaxis in specific cases[14]. Xylitol agents may enhance salivary flow and prevent JRP episodes[1,8]. For patients with sequelae, including recurrent pain, chronic swelling and a decrease in gland function, interventional treatments such as ductal injections or sialendoscopy may be considered, though their availability and efficacy vary[14,17,21].

In this retrospective and descriptive study, we aim to provide valuable insights into the epidemiology, clinical presentation, diagnostic evaluation, and management of JRP in a pediatric population, drawing upon a decade-long experience in a tertiary-level hospital in Portugal. By elucidating key aspects of JRP, our findings seek to inform evidence-based practices, foster interdisciplinary collaborations, and ultimately improve outcomes for individuals affected by this intriguing inflammatory disorder.

METHODS

This is a retrospective and descriptive study. We included all pediatric patients (aged below 18 years old) with the diagnosis of JRP, followed over 10 years and 7 months (from January 1, 2010 until July 31, 2020), in the pediatric unit of a tertiary-level hospital in Portugal. The diagnosis of JRP was based on clinical criteria, considering inclusion criteria: age < 16 years, recurrent unilateral or bilateral swelling, and at least 2 episodes during the last 6 months, as well as exclusion criteria: obstructive lesions, dental malocclusion, Sjogren syndrome and IgA deficiency. Remission was considered if there was an absence of crises for at least 2 years.

The data were collected from medical records and organized into a standardized form design in Microsoft Office Excel 2010. This form was based on international registries and available literature. Demographic information, patient and family history, clinical and laboratory findings, treatment, evolution and complications were assessed. The following parameters were evaluated: age, sex, date of first symptoms, location and number of episodes, need for pediatric emergency care, and ultrasonography findings in the acute phase and later.

RESULTS

A total of 25 patients with PRJ were investigated. The age of onset ranged from 18 months to 11 years, with a median age of four years and two months. A predominance of male patients was observed in 64% of the cases. Family history was positive in only one patient. All patients had been immunized with the mumps vaccine. There was no history of dryness of the eyes, joint pains, swelling or skin rashes suggestive of autoimune disorder. Concerning localization, we found that 84% of the cases display parotitis on one side, with the parotid gland involved in 86% of the cases. All patients had parotid swelling, associated with pain in 68% of cases and fever in 12% of cases. On average, patients experienced two episodes per year (minimum two, maximum six), with symptoms usually lasting eight days (minimum four days, maximum 16 days). During the study period, there were a total of 63 visits to pediatric emergency care. Ultrasonography was performed in 60% of the cases during the acute phase, excluding complications, and in 11% of the cases, an analytical study was carried out, with the need for antibiotic therapy for suspected bacterial infection in five cases (8%). The antibiotics of choice in all cases were amoxicillin and clavulanic acid. All patients were treated with anti-inflammatory therapy, and about half was medicated with xylitol, chewable or aromatic lozenges. During evaluation, the autoantibody profile was positive in one patient (positive antinuclear antibody Witt anti-Ro/SSA and anti-La/SSB negative) and no evidence for autoimmune diseases such as Sjogren´s syndrome or Systemic Lupus Erythematosus was established. Primary immunodeficiency, specifically antibody deficiency, was detected in two patients: a two-years-old boy (IgA 6 mg/dL) and a four-year-old boy (IgA <4 mg/dL) had selective IgA deficiency. Sialography was used only in one patient,

who was suggestive of canal dyskinesia. We also identified one patient with sialolithiasis of the submandibular gland. Ultrasound was performed after the acute episode in 76% of the patients, showing chronic changes in almost 50% of the cases: multiple hypoechoic areas in the glandular parenchyma were observed in 9 cases, chronic sialoadenitis in 3 cases, enlarged intraglandular lymph nodes in 4 cases, and microcalcifications in 3 cases. The average age of children with JRP is 9 years (minimum three, maximum 18), with no associated complications observed until the data. At the moment, we identified that about one-third of patients have JRP with an inconclusive study, three children are still under investigation, and nine pediatric patients are in remission.

DISCUSSION

The retrospective and descriptive study conducted aimed to explore the clinical characteristics, demographic profiles, and management strategies of pediatric patients diagnosed with JRP over a decade-long period in a tertiary-level hospital in Portugal. The findings shed light on various aspects of JRP, including its presentation, diagnostic approaches, treatment modalities, and outcomes. As a diagnostic criteria for JRP, at least three episodes of parotitis were considered in order to avoid false negatives[8].

One notable observation from our study is the predominance of male patients, which aligns with existing literature suggesting a higher prevalence of JRP among males[1,4,6,7,11,17]. The age of onset of JRP ranged widely, underscoring the variable nature of the condition. Despite this variability, the median age of onset was consistent with previous reports, highlighting the typical age range at which JRP manifests in pediatric patients[1,8,16]. According to the literature, the age of presentation is between three months and 16 years[4,6,11,16,23], but it commonly begins between three and six years old and over 10 years old[1,7-9, 11,12,21].

Immunization with the mumps vaccine was universal among the study cohort, suggesting potential avenues for exploring the vaccine's role in preventing or modifying the course of JRP[4,9,12]. The clinical presentation of JRP was characterized by recurrent episodes of parotid swelling, often accompanied by pain and fever, along with clinical findings indicating unilateral involvement of the parotid gland and swelling and pain with well-defined limits in all patients[1,4,6-8,16]. On physical examination, the parotids have well-defined limits and a hard-elastic consistency[7,8,16]. Frequently observed are a nonpalpable jaw angle and the discharge of mucopurulent saliva through the duct papilla upon compression of the gland[17]. Elevation of the earlobe may also be present[7,8,16]. These symptoms, while debilitating for patients, typically resolved spontaneously within a week, consistent with literature indicating durations of two to 14 days[1,8,11,15,17] for symptom resolution[8,11]. Additionally, the literature highlights the recurrent nature of the disease, with an average of one to 20 attacks per year[1,20], although the mean number of episodes is typically around 1.5[17] or three to four times annually[4,8,11]. In our study, the frequency and duration of episodes align with previous findings, highlighting the cyclical pattern of JRP. Diagnosis often occurs in childhood, with many patients expected to experience spontaneous resolution as they age, although JRP may persist into adulthood[4,19].

Diagnostic modalities, including ultrasonography and laboratory tests, played crucial roles in confirming the diagnosis and assessing disease severity[7]. Notably, ultrasonography revealed chronic changes in a significant proportion of patients, highlighting the long-term implications of JRP on glandular parenchyma. Additionally, the diagnosis of JRP was confirmed in the acute phase with ultrasound in 60% of cases, owing to its easy access and sensitivity in detecting changes in the parotid gland, while an analytical study was conducted in an emergency context in 11% of cases, particularly when bacterial co-infection was suspected or if the clinical presentation was severe.

Treatment strategies primarily focused on symptomatic relief and included anti-inflammatory therapy and, in some cases, antibiotics for suspected bacterial co-infections (fever and purulent secretion)[3,14], which occurred in five patients. The first-line antibiotic is a combination of amoxicillin and clavulanic acid[1], yet they are frequently prescribed for primary respiratory pathogens to mitigate further damage to the glandular parenchyma. Additionally, low or standard doses of prophylactic antibiotics have been suggested in cases of immunoglobulin A deficiency[1,20], potentially decreasing the duration of crises[8], although the efficacy of the latter remains unsupported by scientific evidence[12]. The use of xylitol and sialography demonstrated potential benefits in managing JRP-related symptoms and complications[5,12].

While most patients with JRP experienced favorable outcomes, a subset displayed persistent symptoms or inconclusive diagnostic findings, necessitating ongoing monitoring. The identification of underlying conditions underscores the importance of comprehensive diagnostic assessments. JRP can serve as a potential indicator of underlying diseases, highlighting the importance of screening for conditions such as Sjogren's syndrome, lymphoma, HIV infection, and immunodeficiency in all children[1,3,19]. Our study identified the etiology in several cases, including IgA deficiency, sialolithiasis, canalar dyskinesia and autoantibody profile positivity. We also identified a reduction in episodes observed at the onset of puberty, consistent with previous findings[1,4,6-8].

JPR can affect a patient´s social life and school activities[1,24]. Moreover, few patients can develop sequelae such as reccurent pain, chronic swelling and a decrease in gland function. Here, we have not identified any complications related to JRP. Since most of the cases resolve by puberty, reassurance to the family about the benign course of the disease is enough[14].

The limitation of our study are the small sample size of our PRJ patients and the fact that there is no agreed protocol for complementary investigations for our study. This study allowed us to review the practices of the service, namely the review of antibiotic indications in the PRJ, as well as the need to perform imaging and laboratory tests for patients who come to the emergency department with cases of PRJ and the subsequent management.

The rarity of JRP and the difficulty in defining the etiopathology have led to a lack of universal guidelines for its diagnosis and management[9]. The patients are frequently misdiagnosed and undergo inadequate diagnostic and therapeutic treatment. A possible approach protocol for JPR is presented (Figure 1).

CONCLUSION

In conclusion, our study contributes valuable insights into the clinical profile and management of pediatric patients with JRP. By elucidating key aspects of the disease course and treatment outcomes, our findings may inform future research endeavors aimed at optimizing therapeutic approaches and improving patient outcomes in this population (Table 1).

Table 1: Etiopathology of Juvenile Recurrent Parotitis

1.	Obstructive lesions: congenital ductal malformations, stenon´s duct lithiasis, neoplasm
2.	Allergy
3.	Trauma
4.	Infections
a)	Viral infections: EBV, CMV, Herpes simplex b) Bacterial infections from the oral cavity
5.	Hereditary genetic factos
6.	Immunological deficits
a)	IgA deficiency and/or IgG subclasse deficiency b)HIV infection
7.	Rheumatology (Sjogren syndrome; systemic lupus erythematosus, mixed connective tissue disease, sarcoidosis)
8.	Idiopathic (majority)

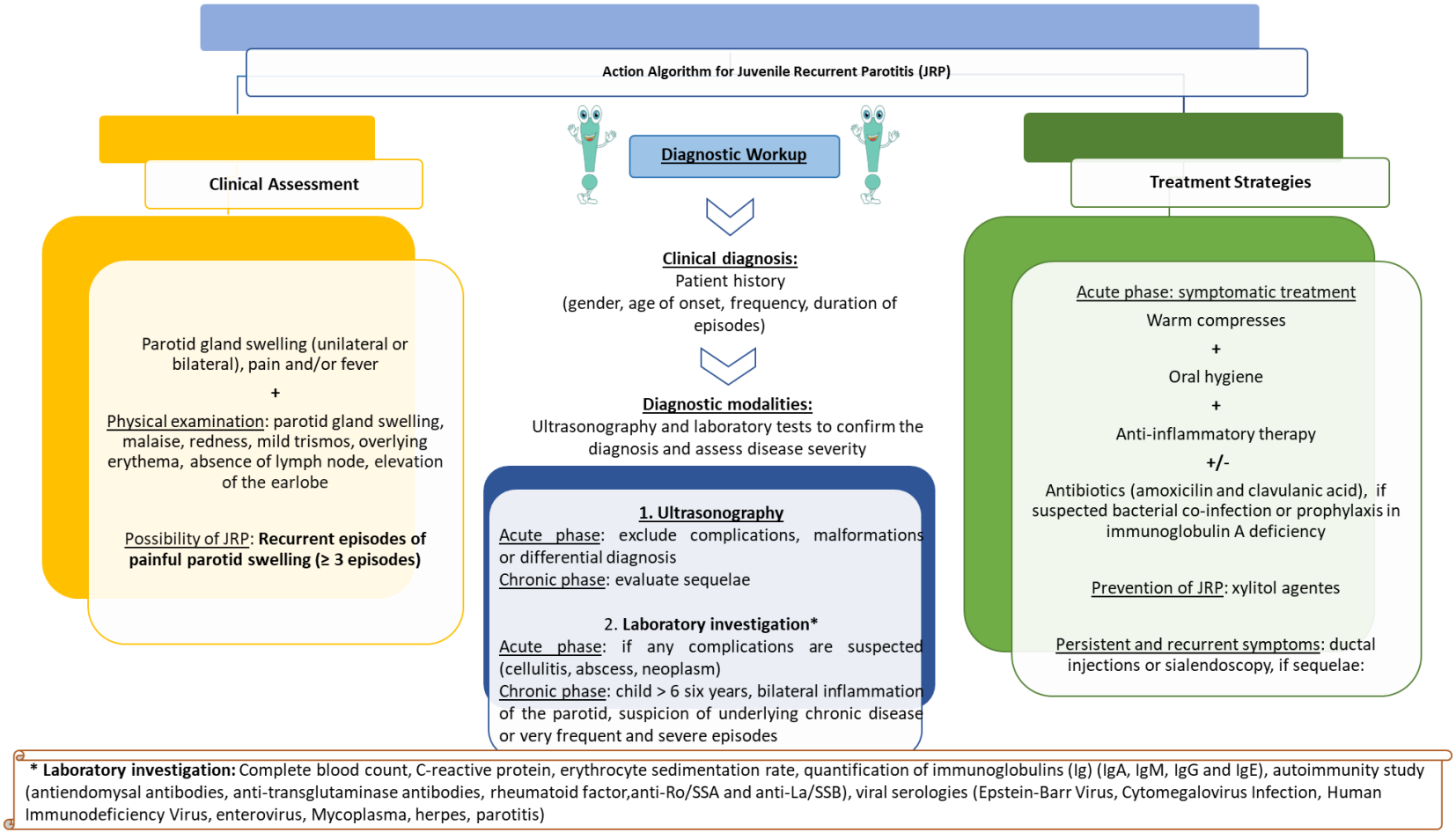

Figure 1: Action Algorithm for Juvenile Recurrent Parotitis (JRP)

STATEMENT OF CONFLICT OF INTERESTS

- The authors declare that there were no conflicts of interest in conducting this work.
- The work was presented at the 1st Digital Pediatrics Conference of the Portuguese Paediatrics Society

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