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Intravenous imunoglobulin treatment and evaluation of autoinflammatory and ımmunodeficiency-associated recurrent parotitis cases in children

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Abstract

Recurrent juvenile parotitis is a rare inflammatory condition characterized by recurrent, non-obstructive, and non-suppurative inflammation of the parotid gland during childhood. Diagnosis of the disease is based on clinical symptoms and laboratory tests. Although cases of recurrent parotitis are rare, various diseases can contribute to its etiology. Case series in the literature have reported diagnoses of immunodeficiency and autoimmune diseases. This study presents five cases diagnosed with autoimmune disease and immunodeficiency, successfully treated with intravenous immunoglobulin.

Keywords: recurrent parotitis, immunodeficiency, autoinflammatory, IVIG

1. Introduction

Recurrent parotitis is an infrequent inflammatory disease characterized by unilateral or bilateral swelling of the parotid gland, presenting with recurrent attacks. It is the second most common disease of the salivary gland after mumps (1). Diagnosis in patients experiencing two or more attacks is generally based on history, physical examination, ultrasound, and elevated serum amylase levels. During physical examination, the opening of the parotid duct is usually dilated, surrounded by white-yellow plaques. Ultrasound is used to confirm the diagnosis by detecting sialectasis, hypoechoic areas, and punctate calcification during the examination (2,3). Although the exact cause of the disease is not fully understood, various etiological factors have been reported in children, including congenital ductal malformations, genetic factors, autoimmune diseases such as Sjögren's syndrome, allergies, sarcoidosis, and immunodeficiencies such as selective IgA deficiency. In adults, it is often associated with HIV (4).

The aim of this study is to focus on the rare recurrent parotitis disease in children and emphasize the potential role of immunodeficiency and autoimmune diseases in its etiology. Additionally, the study will discuss the potential of intravenous immunoglobulin (IVIG) treatment in reducing the frequency of attacks.

2. Materials and Methods

The study included pediatric patients who had experienced at least two clinically confirmed episodes of parotitis, with diagnoses supported by laboratory and imaging findings, and who were evaluated for underlying immunodeficiency or autoimmune conditions.In this retrospective case review, the files of patients who presented to the Department of Pediatric Immunology and Allergy at - Faculty of Medicine were examined, and necessary permissions were obtained from the patients' families and the hospital ethics committee. The evaluation of patients was conducted using a previously established method (5,6). The files of five children diagnosed with recurrent parotitis were thoroughly examined. The diagnosis of recurrent parotitis was confirmed by clinical and ultrasonographic findings in children who had at least two acute non-suppurative parotitis attacks. The age at the onset of each attack, duration, affected gland, and frequency of attacks were recorded for each patient. Additionally, family history was assessed for signs of autoimmune disease (skin rash, dry mouth, and eyes, joint swelling), frequent illnesses, growth retardation, persistent wounds, and vaccine unresponsiveness. Physical examination findings, acute phase reactants (erythrocyte sedimentation rate and serum C-reactive protein levels), serum amylase levels, and immunological function tests (absolute lymphocyte and neutrophil counts, immunoglobulin G, A, M levels) were analyzed. Serum rheumatoid factor, autoantibody profile (antinuclear antibody (ANA), anti-double-stranded DNA (anti-dsDNA) antibodies, anti-RNP antibodies, anticardiolipin, anti-smooth muscle antibody (anti-ASMA), antiphospholipid antibodies, anti-Ro (SS-A), anti-La (SS-B) antibodies), serum complement levels (C3, C4), and infectious markers (anti-mumps IgM, anti-HAV

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IgM, HbsAg, anti-HCV, anti-HIV, anti-CMV IgM, anti-EBV IgM, anti-toxoplasma IgM) were also evaluated.

2.1. Case 1

A 12-year-old male patient experienced recurrent parotitis attacks starting at the age of 6, totaling 14 episodes. The swelling was usually observed in the patient's right salivary gland, and the attacks lasted for 7-10 days. The patient also exhibited symptoms such as swelling, redness, and pain in the hands and feet. There was no consanguinity between the parents. The patient's mother also had similar arthritis and dermatitis complaints. Although the patient did not have familial Mediterranean fever (FMF) mutations, a nod2 mutation (c.2798+158C > T) was detected. Despite repeated empirical antibiotic treatment during parotitis attacks, the attacks persisted. The patient responded well to intravenous immunoglobulin (IVIG) treatment (400 mg/kg/day, every three weeks) and colchicine therapy.

2.2. Case 2

An 11-year-old female patient, whose parents were cousins, experienced her first attack at the age of 9 and had a total of 6 recurrent parotitis attacks.The attacks were concentrated on the right side of the patient. Additionally, elevated liver enzymes, hypothyroidism, and lymphopenia were present. Although serum immunoglobulin values were within normal limits for her age, high levels of antinuclear antibodies (ANA+++) were detected in the tests. Mutations M696V and R202Q were identified in investigations for recurrent fever and joint pain. The patient responded positively to colchicine and IVIG treatment, and her symptoms and liver enzyme levels returned to normal.

2.3. Case 3

A 13-year-old male patient experienced his first attack at the age of two and had a total of 6 recurrent parotitis attacks. The patient's parents were consanguineous. The patient had a history of frequent infections, and his mother had psoriasis. Serum IgG and IgM levels were found to be low for his age. With a diagnosis of common variable immunodeficiency, the patient was started on IVIG treatment. Before the treatment, the patient experienced recurring attacks every 3-4 months, but after the treatment, the attacks significantly decreased, and no attacks were observed in the last three years. The patient was found to have a TNFRSF13B C104R heterozygous mutation through genetic testing.

2.4. Case 4

An 11-year-old male patient, who first presented at the age of 3 with recurrent fever, neck swelling, frequent infections, joint pain, and mouth sores, was evaluated, with no consanguinity between the parent. Streptococcus pyogenes growth was detected in the patient's throat culture. Attention deficit hyperactivity disorder symptoms were observed in follow-ups, and the patient was considered to have pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). Monthly long-acting penicillin treatment was initiated, and psychiatric follow-up was conducted. However, the swelling in the patient's neck continued, and attacks occurred almost every month. During this process, no growth was detected in throat cultures. Familial Mediterranean fever (FMF) and PFAPA syndrome were excluded through tests and steroid treatment. Although the patient's immunological function tests tests were normal, high levels of thyroid autoantibodies were found. Considering autoimmunity and PANDAS, the patient responded positively to IVIG treatment.

2.5. Case 5

A 6-year-old male patient experienced his first attack at the age of 3. The patient, who used medication for epilepsy, had a history of frequent infections, prolonged moniliasis in the neonatal period, and prolonged febrile periods after vaccinations. The patient's sibling had recurrent fever and joint pain, and there was a history of FMF in the family, with the parents being consanguineous.Despite normal immunodeficiency tests, high levels of thyroid autoantibodies were found. Considering autoimmunity and PANDAS, the patient was started on IVIG treatment and showed no attacks during the IVIG treatment period.

Based on the patients' medical history, physical examination findings, and laboratory results, differential diagnoses of allergy, sarcoidosis, and Sjögren's syndrome were considered, but no consistent findings were identified. When evaluating the diagnosis and treatment of our patients, the second case received IVIG treatment due to suspicion of autoimmunity. Similarly, the fourth case underwent IVIG treatment under comparable circumstances. The third case was associated with TACI deficiency, while the fifth case presented suspicion of common variable immunodeficiency. The first case was diagnosed with Blau syndrome associated with a nod2 mutation. Each patient had received various antibiotic treatments (such as penicillin, ampicillin-sulbactam, cefuroxime, etc.) prior to their presentation to our clinic. Following evaluations conducted at our clinic, the patients were administered regular IVIG treatment for approximately 6 months. In cases 1 and 2, colchicine treatment was initiated in addition to IVIG therapy. In case 1, a parotitis attack recurred once after discontinuation of the medication. Due to their diagnosis of CVID, cases 3 and 5 continue IVIG treatment to mitigate the risk of additional infections.

Table 1. Clinical and laboratory characteristics of children diagnosed with recurrent parotitis

Patient	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gender	male	female	male	male	male
Age of Patient	12 years	11 years	13 years	10 years	6 years
Age of First Attack	6 years	9 years	2 years	3 years	3 years
Total Number of Attacks	14	6	6	numerous	4
Attacks Time	7-10 day	7 day	10 day	7-10 day	10 day
Side of Attacks	right	right	bilateral	right /bilateral	right
Tracking Time	1 years	3 years	6 years	7 years	1 years
Leukocyte	11490	15780	9120	8000	16960
ESH (mm/s)	56	21	12	28	70
CRP (mg/dl)	37	48	34	12	144
Amylase (U/L)	266	1530	388	269	386
Autoantibodies	negative	ANA+++	negative	Thyroid autoantibodies positive	negative
Infection Viral Markers	negative	negative	negative	negative	negative
Concomitant Disease	NOD2 mutation (Blau syndrome)	Hypothyroidism, FMF (M694V mutation)	CVID (TNFRSF13B C104R Heterozygous Mutation)	autoimmune thyroiditis	CVID
Treatments	IVIG colchicine	IVIG colchicine	IVIG	IVIG	IVIG
IgG (mg/dl)	1040 (N:907-1958)	895 (N:835-2094)	590 (N:907-1958)	916 (N:835-2094)	610 (N:764-2134
IgA (mg/dl)	94 (N:96-465)	210 (N:67-433)	90 (N:96-465)	74 (N:67-433)	83 (N:70-303)
IgM (mg/dl)	133 (N:83-232)	160 (N:47-484)	54 (N:83-232)	68 (N:47-484)	185 (N:69-387)
IgG Subgroups	normal	normal	normal	normal	normal
Lymphocyte %	%27	%17	%25	%13	%26
T helper (CD3+CD4+ %)	%31 (N:27-57)	%34 (N:27-57)	%36 (N:27-57)	%42 (N:27-57)	%34 (N:26-48)
Cytotoxic T cells (CD3+CD8 +%)	%43 (N:19-38)	%33 (N:19-38)	%17 (N:19-38)	%27 (N:19-38)	%34 (N:20-42)
B cells (CD19+ %)	%13 (N:10-30)	%13 (N:10-30)	%14 (N:10-30)	%10 (N:10-30)	%15 (N:10-27)
Natural killer cells (CD3- 16+56+ %)	%11 (N:8-30)	%10 (N:8-30)	%27 (N:8-30)	%13 (N:8-30)	%9 (N:8-27

(ESH: Erythrocyte Sedimentation Rate, CRP: C-Reactive Protein, N: Neutrophil count, ANA: Antinuclear Antibody, FMF: Familial Mediterranean Fever, IVIG: Intravenous Immunoglobulin, Ig: Immunoglobulin)

3. Discussion

Recurrent parotitis refers to intermittent inflammation of one or both parotid glands. Although its incidence is not precisely known, small case series have been reported in the literature. This condition, more commonly observed in males, typically has an onset age between 3 and 6 years. It usually manifests in episodes occurring every 3-4 months, lasting 4-7 days. Three of our patients were observed to exhibit recurrent parotitis symptoms within this age range (1). However, two of our patients had different onset ages; one experienced initial attacks at 1.5 years, while the other at 9 years. Late-onset cases were also encountered in a series of 20 cases by Ericson et al. (4). Similar to the literature, the ratio of male patients was higher in our series.

Patients with recurrent parotitis experience attacks at least twice. Symptoms observed during these attacks include swelling, pain, fever, redness, and increased warmth in the parotid gland (2). All our patients had signs of swelling and fever in the parotid gland. Diagnoses were confirmed through ultrasound and laboratory tests. In all patients, mumps vaccination had been administered before, and mumps IgM was negative, while IgG was positive. Since mumps-associated parotitis cases can occur in adults, anti-HIV tests were also negative to exclude this condition. Tests for other viral diseases yielded negative results.

Recurrent parotitis cases associated with immunodeficiencies such as selective IgA deficiency, IgG3 deficiency, X-linked hypogammaglobulinemia, common variable immunodeficiency, and autoinflammatory diseases like Sjögren's syndrome have been reported in the literature. However, the exact cause remains uncertain (2, 7). Due to the unclear etiology of recurrent parotitis, there is no consensus on treatment. While many experts do not use antibiotics during acute attacks, the benefit of prophylactic antibiotic use has not been demonstrated.

A prospective case-control study conducted by Wu et al. in patients with juvenile recurrent parotitis (JRP) showed that as age increases, CD4+ levels decrease, while CD8+ T levels

relatively increase. CD4+ T cells are essential components of the immune system, particularly crucial for signaling CD8+ cytotoxic cells that destroy infected cells. Therefore, the disturbance in the CD4/CD8 T cell ratio can lead to infectious or autoimmune diseases (8,9). In the same study, significant differences were found in IgG, IgE, IgA, and C3 levels. The authors suggested that immune function in JRP patients differed from the general population, indicating decreased cellular immunity and insufficient antibody production. They proposed that immunotherapy aiming to improve immune responses systemically and in the parotid gland should be prioritized (8,9).

Intravenous immunoglobulin (IVIG) treatment is among the mechanisms affecting the immune system. Specifically, IVIG has been observed to promote the expansion of CD4+CD25+ regulatory T cells (Tregs), playing a significant role in the control of autoimmune diseases and inflammatory conditions. IVIG also exhibits immunomodulatory effects by suppressing T and B cell activation. It has been demonstrated that IVIG preparations work by directly influencing T cell proliferation and reducing B cell receptor (BCR)-mediated activation of B cells (1,10).

The efficacy of IVIG therapy in autoimmune and inflammatory diseases has been demonstrated in various studies. A long-term study on rheumatic diseases reported that IVIG treatment led to remission in the majority of patients; however, a decrease in treatment response was observed in some cases after seven years (11). Similarly, research on treatment-resistant uveitis has shown that IVIG is an effective and well-tolerated option for controlling inflammation (12). Nonetheless, evaluations in pediatric rheumatology patients have revealed that approximately half of the cases experienced mild to moderate adverse effects such as headache, nausea, and aseptic meningitis following IVIG administration (13). Additionally, rapid infusion rates and inadequate hydration have been associated with serious complications such as renal failure and thromboembolic events. Therefore, during long-term use of IVIG therapy, it is recommended that both clinical efficacy and potential adverse effects be closely monitored (14).Cases 2 and 4 from our study were treated with IVIG due to suspicions of autoimmunity, case 1 with Blau syndrome associated with nod2 mutation, case 3 with TACI deficiency, and case 5 with suspected common variable immunodeficiency. After treatments, only case 1 experienced two more attacks at longer intervals, while the others had no further attacks. In cases with underlying autoimmunity or immunodeficiency, as indicated in our study, IVIG treatment resulted in a reduction in the number and frequency of attacks. These findings highlight the importance of immunological and genetic evaluation in cases of recurrent parotitis and suggest that IVIG and colchicine treatments can be effective in preventing attacks.

Recurrent parotitis cases in children may be associated with autoinflammatory diseases and immunodeficiency conditions. Understanding the underlying causes of this disease is critically important for determining effective treatment strategies. IVIG treatment can be considered as a treatment option in recurrent parotitis cases associated with autoinflammatory diseases and immunodeficiency in children. This treatment can modulate the immune system, reduce inflammation, and balance immune responses. However, further research is needed to better understand the role of IVIG in the treatment of recurrent juvenile parotitis (JRP) in children. Future studies should focus on better understanding the reasons for recurrent parotitis in children and developing more effective treatment methods. Continued research in this field will contribute to a better understanding of the disease and the development of treatment approaches.

Our study suggests that in children with recurrent parotitis and underlying immunodeficiency or autoimmunity, IVIG may be an effective alternative in cases unresponsive to first-line treatments. Therefore, early immunological evaluation and consideration of IVIG in resistant cases are clinically important.

This study has several limitations. First, as it is a retrospective and observational study, it is not possible to establish a causal relationship. The small sample size limits the generalizability of the findings, particularly regarding the efficacy and safety profile of IVIG therapy. Additionally, the lack of a standardized clinical scoring system for evaluating treatment response may introduce subjectivity into the assessments. The duration of long-term follow-up varied between cases, and long-term outcomes could not be fully evaluated in some patients due to limited observation periods. Moreover, concomitant treatments such as colchicine or supportive therapies may have influenced the treatment outcomes, representing a potential confounding factor. Therefore, these findings should be supported by larger, prospective and controlled studies to validate their significance.

Conflict of interest

The authors declared no conflict of interest.

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None to declare.

Authors' contributions

Concept: M.U., T.A., Design: M.U., T.A., Data Collection or Processing: M.U., T.A., Analysis or Interpretation: M.U., T.A., Literature Search: M.U., T.A., Writing: M.U., T.A.

Ethical Statement

Approval was obtained from Ondokuz Mayıs University Clinical Research Ethics Committee, the study started. The ethics committee decision date is 27/02/2020 and the number of ethical committee decisions is 2020/93.

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