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RESEARCH ARTICLE

RECURRENT APHTHOUS STOMATITIS: A CASE SERIES

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ABSTRACT

Recurrent Aphthous Stomatitis is the most frequent ulcerative disorder observed in the oral cavity. The aetiology is unknown, but several predisposing factors have been identified as possible causes. These including local, immunologic, allergic, genetic, nutritional or microbial current events. In most cases the disorder is localized but in others, it can be a clinical sign of systemic diseases such as Behçet's disease , or gastrointestinal disorders (Celiac Disease, Crohn's disease, ulcerative rectocolitis) or congenital and acquired immunodeficiency (including HIV infection) and such conditions should therefore be sought and excluded. Here we presented our experience of twenty-one subjects aged between 0 and 12 years evaluated over a period of two years. In this study we aimed to define the clinical features of aphthous ulcers in children with accompanying clinical and laboratory findings supposed to be related to the disease. In our experience one was affected by periodic fever aphthous stomatitis pharyngitis , two were affected by Beçhet's disease and one by Crohn's disease.

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INTRODUCTION

Recurrent Aphthous Stomatitis is the most common multifactorial disorder of the oral cavity, characterized by recurrent painful ulcers, these present a well-defined erythematous margin, yellowish-gray pseudomembranous center and are painful (Preeti *et al*., 2011). Recurrent Aphthous Stomatitis (RAS) has 3 main presentations: major (MaRAS), minor (MiRAS), or herpetiform (HU) ulcers (Preeti *et al*., 2011; Akintoye, 2005; Rogers, 2003):

- **Major RAS:** the aphthous lesions exceed 10 millimeters, a number of lesions ranging from 1 to 10, considerably painful, with a tendency to heal with scarring and may last more than 30 days;
- **Minor RAS:** the aphthae have a size of less than 10 millimeters, last for about 4 -14 days, without scarring;
- **Herpetiform ulceration:** is uncommon in childhood, manifesting with several little aphthae (2-3 millimeters) with irregular and often coalescent edges (Tab.1).
- The ulcers mainly affect lips, cheeks, gums and seldom the palate.

A further classification based on gravity and duration is "simple" and "complex". Table 2 illustrates the differences between "simple", the most common, and "complex" the less frequent variant of RAS (Rogers, 2003). Recurrent Aphthous Stomatitis affects between 5 and 25% of the general population and according to some studies even up to 40% of children.(4) Such differences are strictly connected to the origin of the examined groups and populations as well as of the studies design and methodology (Natah *et al*., 2004; Scully , 2008; Liang , 2012). Although the aetiology is unclear, a relationship with both local and systemic causes has been recognized. The main causes are reported in table 3. and can be classified into hereditary diseases (e.g. bullous epidermiolysis), microbial diseases (viral, bacterial or mycotic), trauma (dental equipment), nutritional deficits (iron, folic acid, zinc, B1, B2, B6, B12), haematological diseases, autoimmune diseases (e.g. Crohn's disease, Celiac disease, Behçet's disease, Systemic lupus erythematosus, lichen planus, Dermatitis IgA linear), etc. The role of genetic factors in the etiopathogenesis of RAS has been confirmed by the results of currently performed studies of relatives and twins patients, where the positive family history

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of the disorder was reported in 24-46% of cases (Akintoye, 2005). A high frequency of specific HLAs have been identified in RAS patients: including HLA-A33, HLA-B35, HLA-B51 and HLA-Dr7 (Albanidou-Farmaki *et al*., 2008). The genetic risk factors that may modify the individual susceptibility in RAS patients include various DNA polymorphisms, localized in the human genome, especially those related to the alteration of the metabolism of interleukins (IL-1β,IL-2, IL-4, IL-5, IL-6, IL-10, IL-12), interferon γ and TNFα (Natah et al., 2004 and Najafi et al., 2005). It has been shown that genetically engineered triggering factors lead to a dysregulation of the production of cytokines with excess of proinflammatory and reduction of anti-inflammatory factors (Bazrafshani *et al*., 2002). Recently some studies have identified genetic polymorphisms related to immunological mechanisms in the production of interleukine-2 and interferon-γ as often reported in some autoinflammatory disorders (Najafi *et al*., 2015).

Several studies report a higher prevalence of the idiopathic type even if several etiological factors may be presumable. In any case this type of RAS must be differentiated from some systemic diseases in which the aphthous lesions may be associated to other factors during the course of the disorder or may even precede the disease by several years (Akintoye *et al*., 2014). The Behçet's disease is the systemic disease presenting as main sign a recurrent stomatitis with major or minor aphthae and which may precede the onset of other signs (ocular, cutaneous, vascular, articular, neurologic) even by some years (Hatemi *et al*., 2009). In other ones the RAS may also be present with variable frequency depending on the stage of the disease. Other disorders which can be associated with RAS are: cyclic neutropenia, celiac disease, periodic fever aphthous stomatitis pharyngitis (PFAPA), linear IgA disorder, the mucous membrane pemphigoid, and two disorders of gastrointestinal trait, Crohn's disease and the ulcerative rectocolitis. In this study we aimed to define the clinical features of aphthous ulcers in children with accompanying clinical and laboratory findings supposed to be related to the disease.

Clinical cases: With the approval of ethics committee from Department of Clinical and Experimental Medicine of University of Catania (Approval Number 234678, OVE-Policlinico) and the Informed Consent of the parents of children less than 18 years old, we started retrospective study including twenty-one patients under 18 year who were admitted to the Acireale Pediatric Unit, Catania (Italy) between January 2012 and May 2014 with more than three episodes of RAS for year. The diagnosis was based on clinical examination. A board of specialists (a paediatrician, a dermatologist, a dentist, an oculist , an immunologist, etc.) evaluated demographic characteristics, the average number of aphthae per year, type of ulcers, duration of the disease, scarring after genital ulcers, papulopustular and nodular lesions, ocular disease, pathergy test results, family history, and related diseases. All patients were subjected to laboratory tests such as defining haematologic (blood count, ferritin, vitamin B12 levels), immunological (serum immunoglobulin levels, ANA, ASCA, dsDNA) and infectious parameters (HIV, CMV, EBV). Oral ulcers were classified as major (diameter > 10mm), minor (diameter < 10 mm), or herpetiform (2-3 mm). Dermatologists evaluated the presence of papulopustules or skin nodules. The pathergy test was performed on the flexor surface of the forearms by pricking three different areas using a disposable 20-gauge needle intradermally.

RESULTS

Twenty one patients were included in the study divided into two groups (Table 4). One group of infants (0-2 years) and another of preschool and school age children (3-12 years). Group 1: three patients were affected by minor aphtae. No systemic disorders were reported among these patients. However a year later one of them developed a PFAPA disease. Group 2: family history was positive in 23% of cases. Pathergy test and laboratory findings were normal. In two patients the pathergy test became positive in the third year of life. We have reviewed these two patients after an observational period until they became adult and a diagnosis of Behcet's disease was made. There was no significant relationship between the number of aphtae per year or the duration of the disease and other mucocutaneous findings, ocular disease or development of pathergy.

DISCUSSION

Recurrent Aphthosis Stomatitis is the most common disease of the oral cavity in childhood. Some studies reported a frequency of 46% in children (Preeti, 2011; Akintoye, 2005; Akintoye, 2014). In children as well as in adolescents, it occurs more frequently in its Minor form and it is rarely associated with Maior type ulcers. Having to distinguish between primary and secondary forms, frequent observations and laboratory tests are needed. On the other hand, it is necessary and important to be able to diagnose diseases that usually occur with recurrent aphthous stomatitis, such as celiac disease, Crohn's disease, cyclic neutropenia and Behçet's disease in time. These patients recurrently experience a period of poor quality of life, limiting nutrition and loss of school days. In the infant group (0-2 y), no alterations were found either in laboratory data or during the observation period, and no clinical or laboratory manifestations related to local or systemic disease were reported. Only one was subsequently diagnosed with PFAPA due to the appearance of periodic fevers associated with RAS. The fever is rare in RAS but when present it indicates an infectious disease or when a periodic fever is recurring. Two patients in the second group have been diagnosed with BD after the end of an observation period during the post-adolescent age. In both children at the early stages there were no mucocutaneous manifestations beyond RAS nor ocular pathology, but the aphthous stomatitis was classified as complex according the criteria of International Conference on Behcet's Disease (Edgar, 2017) and after the years of observation the pathergy test became positive.

A patient was diagnosed with Crohn's disease due to the simultaneous presence of anemia and weight loss. The endoscopic investigation and histological features confirmed the diagnosis. In group 2, the correlation with systemic disease was calculated at 14% of all RAS. Our observational data and those of the literature lead us to consider unnecessary to investigate subjects with RAS that are under 2 years old with the only exclusion of PFAPA or cyclic neutropenia. The second group ought to be subjected to appropriate clinical investigations and clinical observations with the aim to exclude at least three diseases: Crohn's Disease, Celiac Disease and Behçet's Disease, as well as detecting any other local causes. In the first group the treatment (see Tab. 5) of infants was only topic with the use of antiseptic, anti-inflammatory and antibiotic drugs.

Table 1. .Morphological classification adapted from Preeti L. (1).” Recurrent aphthous stomatitis” *J Oral Maxillofac Pathol* 2011

	Minor RAS	Major RAS	Herpetiform RAS
Gender	M=F	M=F	M=F
Morphology	Round or oval Pseudomembranous gray/white Erithematous halo	Round or oval Pseudomembranous Erithematous halo	Small, irregular, coalescent contours
Localiztion	Lips, cheeks, tongue	Lips, cheeks, tongue, gums	Lips, cheeks,gums, tongue
Number of lesions	1-5	1-10	10-100
Size	<10 mm	>10mm	2-3 mm
Prognosis	Healing without scarring in 4-14 days	Duration > 6 weeks Common scarring	<30 gg Uncommun scarring

Table 2. By International Conference on Behçet’s Disease (2003)

Simple Aphthosis	Complex Aphthosis
Common	Uncommon
Episodic	Episodic or continuous
Short-lived lesions	Persistent lesions
Few lesions	From few to many lesions
Three/six episodes per year	Frequent or continuous Ulcerations
Prompt healing	Slow healing
Pain	Notable pain
Little disability	Disabling
Limited to oral cavity	May affect genitals

Table 3. Acute and chronic causes of RAS

Hereditary diseases	Bullous epidermolysis
Viral, bacterial and mycotic diseases	Coxsackie, Herpes Simplex, Cytomegalovirus, HIV, Tbc, Blastomyces dermatitis, Candida
Nutritional deficits	Iron, folic acid, zinc, B1, B2, B6, B12
Trauma	Dental equipment
Haematological	Anemia, neutropenia, hypereosinophilic syndrome
Recurrent fevers	Cyclic neutropenia, PFAPA, autoinflammatory diseases
Autoimmune diseases	Crohn’s disease, Celiac disease, Behçet’s disease, Systemic lupus erythematosus, lichen planus, Dermatitis IgA linear
Others	Mouth and genital ulcers with inflamed cartilage syndrome (MAGIC syndrome), hormonal, neoplastic disease

Table 4. Demographic and clinical characteristic of 21 patients

		0-2 yrs n (%)	3-12 yrs n (%)
Gender	Male	2 (9)	8 (38)
	Female	1 (4)	10 (47)
Type	Major	0	2 (9)
	Minor	3 (14)	16 (76)
	Herpetiphorm	0	0
Average duration		7 days	12 days
Aphthae scars	No	No	0
Genital ulcers	No	No	0
Ocular disease	No	No	0
Pathergy test Positive		No	3 (14)
Associated diseases	Cyclic neutropenia	No	No
	PFAPA	1 (4)	No
	Behçet’s disease	No	2 (9)
	Crohn’s disease	No	1 (4)
	Celiac disease	No	No
Simple		3	15 (71)
Complex		No	3 (14)

Table 5. Suggested treatment for RAS

First line	Anesthetics	Lidocaine, Benzydamine
	Anti-inflammatories	Diclofenac, Amlexanox
	Steroids	Fluocinolide acetonide Triamcinolone acetonide Clobetasol propionate
Second Line	Prednisone 25mg daily	
Third Line	Antimicrobials	Penicilline G Dapsone 25 mg/day x 3 days
	Anti-inflammatories	Colchicine 0,5 mg/dayx7 days Pentoxifylline 400 mg 3x/day for one month
Fourth Line	Immunomodulators	Thalidomide 50-100 mg daily Levamisole 150 mg 3x/week x 6 months

In the second group, the treatment went from a first step which classified the type as reported in Fig.1, to a second and a third step, especially in cases of complex RAS (Edgar *et al*., 2017), which applied a partial reduction in amplitude and duration of aphtae. In the present study it was not necessary to reach the fourth step which was subsequently carried out in the cases of Behcet's disease. Biological therapy has been successfully performed in the case of Crohn. Our case series have some limitations, due to the presence of a small sample of examination, and also for the actually little knowledge in autoimmune disease in childhood. In conclusion, RAS is not very frequent in subjects under the age of 2, where the therapy is exclusively local. RAS is more prevalent in pre-adolescent and adolescent age, a time when it is necessary to distinguish the different systemic illnesses which are likely to have low frequency. Systemic illnesses presenting particularly severe forms of aphthae that, by location, entity, duration, and general symptoms are complex require more selective investigations and therapies.

Abbreviations: BD (Behçet disease), HU (herpetiform ulceration), RAS (recurrent aphtous stomatitis), , MAGIC syndrome (Mouth and genital ulcers with inflamed cartilage), MaRAS (Major recurrent aphtous stomatitis), MiRAS (minor recurrent aphtous stomatitis), PFAPA (periodic fever aphtous stomatitis pharyngitis).

Informed Consent: Written informed consent was obtained from patients' parents who participated in this case.

Conflict of Interest: No conflict of interest was declared by the authors.

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