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Marshall syndrome in children referred to specialist clinic of Imam Khomeini Hospital of Ilam, Iran, 2012

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ABSTRACT

Periodic fever syndrome is a self-inflammatory disease. Since the disease is benign and self-limiting, the present study aimed to achieve a model to detect and differentiate it from other infectious diseases .In this study all children residing in Ilam who were suspected of Marshall Syndrome were examined. We chose a sample comprising children referred to Imam Hospital clinic of Ilam in 2012. Inclusion criteria consisted of more than three periods of fever without a source of infection, fever periods shorter than 5 days and repeated at intervals of about one month .The collected data were analyzed using SPSS software 16. We used both of descriptive and inferential statistics, Kolmogrov smirnov, Chi-square. Significance level of $P \leq 0.05$ was considered. The average of patients' age was 4.9 ± 1.8 months and their gender perception was 85.7% male and 14.3% female. In this study the average age of symptoms emergence was 48.33 ± 23.25 month. The average of fever periods in surveyed patients was 4.09 ± 0.88 days (minimum 3 days & maximum 5 days) and the intervals between fever periods was 40.23 ± 16.84 in average. The applied treatments in this study were Prednisolone and Ttonsillectomy. There was significant relationship between age and the symptoms ($P<0.007$). By having a true perception of Marshall Syndrome using diagnosis criteria, we could prevent uncontrolled prescription of antibiotics and their possible side effects, and it is a positive step towards reducing healthcare costs.

Keywords: Epidemiology, PFAPA, Marshall Syndrome, Iran, Ilam.

INTRODUCTION

Marshall Syndrome is an autosomal recessive disorder that all nations are concerned about [1, 2]. Periodical fever syndrome is one type of inflammatory diseases. In this syndrome, inflammatory protests, auto-antibodies or spontaneous activity of or T cells cannot be seen [3, 4]. The most common type of these fevers is periodically fever with Aphthous Stomatitis, Pharyngitis and adenitis (PFAPA). Marshall Syndrome was reported first by Garry Marshall et al with unknown etiology in 1987-89 [5, 6]. Ages 2 to 5 years is suggested as the most common age of diagnosis of Marshall Syndrome in which the temperature is about 39 degrees and occurs periodically and at regular intervals [7]. Studies indicate that the prevalence of this syndrome is more in men than women [8, 9, 10].

Pathogenesis of periodically fever is unknown. But increased levels of immune cytokines such as TNF-α, IL-18, IL-6 and IFN-α during periods of fever have been reported [11, 12, 13]. The results suggest that the cellular response of periodical fever is different from infectious diseases. During a period of fever, Monocytes increased while Eosinophil and lymphocytes decreased [13, 14]. Also from other causes of periodical fever Periodical Neutropenia can be noted in which the fever attacks are spotted every 24-18 days with lowest Neutrophil (<500 mm) and usually, fever attacks improve with increasing age [15, 16]. Fever is the main symptoms of periodical fever, and it occurs suddenly. Fever is usually accompanied by chills. Also, other symptoms such as fatigue, restlessness, and Aphthous ulcers may be seen in the first few days of fever and will remain for 3 to 6 days, and then the temperature returns to the normal state suddenly. Rarely does fever last for more than 7 days and the average of time between periods is 2/28 days (between 26-30.4 days) [11]. Since Periodical fever is a benign and self-limited disease, the purpose of the present study is achieving one model for detection and differentiation of Marshall syndrome from other infectious diseases. This is a way that can prevent excessive prescription of antibiotics. Also it can reduce the concern and confusion of parents. Since the Marshall syndrome is a newly-emerged disease, this study can provide a diagnosis and treatment plan method for physicians.

MATERIALS AND METHODS

In this cross-sectional study all children suspected to have Marshall Syndrome referred to Specialist Clinic of Imam Khomeini hospital of Ilam in 2012 were examined. The possible number of patients likely to refer in current study was 20 samples. Inclusion criteria of this study included: coming down with more than three periods of fever without a source of infection, periods of fever shorter than 5 days and repeated fever about one month, and the exclusion criteria of this study included: Increased ESR, CRP, The existence of Leukocytosis without fever during those periods, and the existence of Leukopenia during periods of fever. The demographic characteristics of the patient were recorded at first. Then the former background of the disease (SLE, EBV, HIV, HAV, and Vasculitis) was assessed by standard tests. After the diagnosis of Marshall Syndrome, one dose of Pprednisolone was given, and 24 hours later the patient was seen in order to track the therapeutic effect of prednisone. ESR, CRP and WBC tests were conducted for all participants in feverless period.

Statistical analysis:
After collecting data, statistical analysis was done by using descriptive statistics and Kolmogorov-Smirnov, Chi-square and ANOVA tests in SPSS software (version 16) and the significance level of the test was considered 0.05.

RESULTS

The average age of the patients was 8.1 ± 9.4 months. 85.7 % of participants were male and 14.3% were female. The average period of fever in examined patients was 0.88 ± 4.09 days (minimum 3 days and a maximum of 5 days) and the intervals between periods of fever was16.84 ± 40.23 days. The prevalence of Pharyngitis in patients with Marshall Syndrome was 42.9%, Stomatitis Aphthous was 14.3 %, and the prevalence of cervical Lymphadenopathy was 4.8 %. The relationship between CRP and fever are shown in Tables 1 and 2. There was significant correlation between age and WBC and fever ($p<0.04$). The mean WBC based on age is reported in Table 3. The mean PMN based on age with or without fever is reported in Table 4. In the current study, the ESR was significantly associated with fever and the age of the children ($P<0.02$) (Table 5). There was a significant relationship between age and the symptoms ($P<0.007$).

DISCUSSION

Periodically fever is a group of diseases that fall into the category of inflammatory disease. The whole course of disease is 5.1 to 5.9 years [17]. Concerning the diagnostic criteria of inflammatory diseases, it should be noted that they may overlap with other autoimmune diseases or diseases with recurrent infections. In this study, some clinical and laboratorial findings in Marshall Syndrome`s children with fever and without fever periods were studied. In the present study, most of the patients were male as it was observed in previous studies [11, 19, 18], and it calls for further studies in respect of the role of genetic factors in this syndrome. The mean age of the patients was 1.8 ± 4.9 months, which is the most common age of affected children to fever syndromes. Another study confirms the results of our study [10]. In some cases, the details of Marshall's syndrome in children are different from higher age group in terms of the time spent and the presence of fever. The mean age of onset of symptoms is 23.25 ± 48.33 months. Thomas et al indicated that age average of patients in the population studied, was 2.8 years [11]. In Feden study was

reported that the mean age of the Marshall Syndrome patients was 39.6 months [12]. Although some studies, have been reported that the age average of onset of symptoms was less than it and the age is about 15, 12 and 22 months [13, 14 and 20]. Average period of fever in evaluated patients was 0.88 ± 4.09 days (minimum 3 days and a maximum of 5 days) and the intervals between periods of fever was16.84 ± 40.23 days. The results of this study is accordance with previous findings [20, 21 and 22] but in Marshall et al study s Periods of time without fever was more than other studies. Actually,the period of without fever disease is different [13]. In this study, the prevalence of Pharyngitis in patients with Marshall Syndrome was 42.9 % that this result is consistent with other study (65-96%)[11, 13, 20 and 21]. Result of our study indicated that prevalence of Aphthous Stomatitis is 14% and this result has accordance with other study [9, 11, 14 and 21]. The prevalence of cervical Lymphadenopathy 4.8% was reported, while other studies indicated higher prevalence of cervical Lymphadenopathy(77-61%) in patients with Marshall syndrome [11, 13, 20 and 21]. In this study, like previous studies, measuring changes of CRP during the periodically fever and without fever periods in patients with Marshall Syndrome was observed a significant increased in CRP[14], that this result Indicated the interference of inflammatory factors in the onset of symptoms in this syndrome.

Table 1: prevalence of CRP in patient with fever periods

CRP in with fever periods	No	Percent
Negative	*2*	*9.5*
+	*7*	*33.3*
++	*10*	*47.6*
+++	*1*	*4.8*
++++	*1*	*4.8*
Total	*21*	*100*

Table 2: prevalence of CRP in patient without fever periods

CRP in without fever periods	No	Percent
Negative	*19*	*19*
Positive	*2*	*2*
Total	*21*	*100*

Table 3: Mean and CV of count of WBC in periods with or without fever according to age

	Age (Month)	Count	Mean	CV	P
WBC in periods with fever	24-38	6	14233.33	3155.1	0.04
	38-52	3	8100	4371.49	
	52-66	4	9400	6494.61	
	66-80	3	8233.33	8863.59	
	80-94	5	5420	2968.5	
WBC in periods without fever	24-38	6	5666.66	917.96	0.11
	38-52	3	7400	200	
	52-66	4	5850	759.38	
	66-80	3	5466.66	550.75	
	80-94	5	6840	650.38	

Table 4: Mean and CV of count of PMN in periods with or without fever according to age

	Age (month)	Count	Mean	CV	P
PMN in periods with fever	24-38	6	70.33	8.01	0.88
	38-52	2	57	18.38	
	52-66	4	73.75	11.35	
	66-80	3	65	0.000	
	80-94	5	68.2	9.33	
PMN in periods without fever	24-38	6	47.16	6.4	0.02
	38-52	3	58.66	8.08	
	52-66	4	36.75	4.57	
	66-80	3	54.33	8.14	
	80-94	5	56.4	7.53	

Table 5: Mean and CV of count of ESR in periods with or without fever according to age

	Age(month)	Unit	Mean	CV	P
ESR in periods with fever	24-38	6	39.16	10.34	0.02
	38-52	3	30	8.66	
	52-66	4	45.5	9.88	
	66-80	3	22.66	19.75	
	80-94	5	49.4	12.52	
ESR in periods without fever	24-38	6	14.16	2.71	0.1
	38-52	3	12	2	
	52-66	4	12.75	0.957	
	66-80	3	8.66	1.52	
	80-94	5	10.4	1.94	

CONCLUSION

Since the Marshall syndrome is known more than two decades, and this disease is emerging, there is no sufficient knowledge about it. A correct understanding of Marshall Syndrome can prevent the uncontrolled prescribing of antibiotics and their complications and be a positive step in reducing healthcare costs.

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