

Significance of MCP-1 in predicting the short-term recurrence of primary intussusception in children

An observational study

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Abstract

To evaluate the relationship between the expression level of (MCP-1) in peripheral blood and the short-term recurrence of primary intussusception in children, a retrospective analysis of children with primary intussusception under ultrasound-guided hydrostatic reduction in our hospital from June 2019 to June 2021, a total of 412 cases, 37 cases of short-term recurrence. Enzyme-linked immunosorbent assay was used to detect the expression of MCP-1 in peripheral venous blood; receiver operating curve (ROC) was utilized to evaluate the diagnostic efficacy of MCP-1 in predicting short-term recurrence; logistic regression analysis of risk factors for recurrence. MCP-1 increased in the peripheral blood of children with short-term recurrence ($P < .05$). Logistic regression analysis found that increased MCP-1 was a risk factor for recurrence; ROC showed that 23.24 ng/mL was used as a cut-off value. The sensitivity of MCP-1 for predicting the recurrence of intussusception in children is 82.14%, and the specificity is 75.67%. In primary intussusception, the expression of MCP-1 in the peripheral blood of children with short-term recurrence is raised. Elevated expression of MCP-1 is a risk factor for predicting short-term intussusception recurrence and has certain clinical significance.

Abbreviations: IL-6 = interleukin-6, MCP-1 = monocyte chemoattractant protein-1, ROC = receiver operating curve.

Keywords: Children, Monocyte chemoattractant protein-1, Primary intussusception

1. Introduction

Primary intussusception is common in children under 2 years old and is the most frequent acute abdominal disease in this age group.^[1] In China, according to some scholars reported, the cost of curing intussusception was about 1213.50–1857.61 US dollars.^[2] Color Doppler ultrasound is the primary choice for diagnosing intussusception. The success rate of air enema or water enema under color Doppler ultrasound monitoring to reset intussusception is over 90%, but some children are at risk of recurrence. Recurrence within 72 h is called early relapse.^[3] 2%–15.4% of children with intussusception may have a recurrence, according to statistics.^[4] If the recurrence is not found in time, it will often cause serious consequences. In severe cases, intestinal necrosis or even life-threatening may occur.^[5] It is now generally believed that changes in the peristaltic rhythm of the bowel will lead to intussusception, and the proliferation of submucosal lymph nodes in ileocecal caused by enterovirus infection is an important cause of the disease.^[6] Maintaining normal movement of the bowel is a complicated process involving the

coordination of multiple immune, neurological, and endocrine systems. It has been proved that the immune and inflammatory response of the bowel can change its movement rhythm.^[7] Scholars have found that inflammation played a critical role in the occurrence and development of intussusception in children.^[8] Monocyte chemoattractant protein-1 (MCP-1) plays an important cytokine that mediates inflammation.^[9] This article examined the expression of MCP-1 in the serum of children with acute intussusception, hoping to provide a reference for forecasting short-term recurrence of children with acute intussusception from the serological test indicators. At the same time, it can reduce the economic burden of primary intussusception.

2. Patients and Methods

2.1. Patients

The children with primary intussusception admitted to our hospital from June 2019 to June 2021 were collected, and the inclusion criteria were as follows: Children with primary

The authors have no conflicts of interest to disclose.

The datasets related to our study are available from the corresponding author on reasonable request.

Our study was approved by the institutional review board of The First People's Hospital of Lianyungang and according to the Helsinki declaration. All participants' parents in this study gave written consent before enrollment. Participants' data were considered confidential and no extra cost was imposed on our participants.

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acute intussusception confirmed by color Doppler ultrasound, with typical “concentric circle manifestations”; Successful reduction of water enema under color Doppler ultrasound monitoring; Parents agreed to this study and signed a written informed consent form. Exclusion criteria: Secondary intussusception; Small intussusception; Contraindications of water enema to receive surgical treatment; Children with failed water enema reduction; Children with recurrent without short-term recurrence; Parents refused to sign this study' Children with a consent form. The study was authorized by the ethics committee of The First People's Hospital of Lianyungang and followed the Declaration of Helsinki. The patients who participated in this study signed the written informed consent by legal guardians.

2.2. Experiments

After the child was admitted to the hospital, 4 mL of peripheral venous blood was collected immediately, placed in a heparin anticoagulation tube, and sent to the central laboratory. After being placed at room temperature for 30 min, it was centrifuged at 3000 r/min for 10 mL, plasma was separated, and pipetted up. Put the clear liquid into the EP tube and store it in a refrigerator at -80°C . MCP-1 and interleukin-6 (IL-6) were determined by an enzyme-linked immunosorbent assay kit (Becton Dickinson), and the operation was carried out following the instructions of the kit. The microplate reader measures the optical density value and obtains the concentration of the specimen.

2.3. Statistical analysis

SPSS25 and Graphpad Prism8 were used for data analysis, measurement data were expressed as mean \pm standard deviation, and

a *t*-test was used for comparison; categorical variables were expressed by the number of cases (n), and χ^2 or Fisher's exact test was used for comparison; response operating curve (ROC) to evaluate the diagnostic value of MCP-1; logistic regression analysis of risk factors for recurrence. Two-sided *P* values $<.05$ were considered to represent statistically significant differences.

3. Results

Through strict inclusion and exclusion criteria screening, a total of 412 children were enrolled in the study, including 37 short-term recurrences and 375 nonrecurrent cases. It can be found that short-term recurrence is related to age, presence or absence of blood in the stool, the position of the cap, and presence or absence of previous seizures ($P < .05$) (Table 1). The results showed that the concentration of MCP-1 in the peripheral blood of children with primary intussusception without recurrence was 16.78 ± 10.29 pg/mL, while the concentration of short-term relapses was 34.65 ± 14.58 pg/mL, and the difference was statistically significant ($P < .05$) (Table 2). Through ROC analysis, the results demonstrate that the area under the curve of MCP-1 for diagnosing short-term recurrence of intussusception in children is 0.843, and the best cut-off value is 23.24 ng/mL. This value is the sensitivity of predicting the recurrence of intussusception in children. It was 82.14% and the specificity was 75.67% (Fig. 1). By measuring the expression of MCP and IL-6 in 37 children with short-term recurrence of intussusception, linear regression analysis found that the expression levels of MCP-1 and IL-6 in peripheral blood showed a positive correlation ($r = 0.46$, $P = .003$)(Fig. 2). Five indicators with statistical differences in short-term recurrence, including age, presence or absence of blood in the stool, the position of the cap, the presence or absence of previous seizures, and the expression of MCP-1, were included, and a logistic regression model was established. The age of the child, the position of the cap, the presence or absence of previous attacks, and MCP-1 are all factors for the short-term recurrence of primary intussusception ($P < .05$), and the statistical difference of MCP-1 is the most significant (Table 3).

4. Discussion

Primary intussusception is a common acute abdomen disease in children, and it is also the most common intestinal motility disorder that needs to be dealt with in pediatric surgery. Although the cause of its onset has not been completely determined, it is now believed that its main pathophysiological change is the intestinal tract contractures and diastolic dysfunction is related to children's diet, infection, and immune status.^[10] At present, the preferred treatment method is air enema or color Doppler ultrasound monitoring water enema.^[11] After successful reduction, an important point that bothers clinicians is the recurrence of intussusception. Similarly, the cause of the recurrence remains unclear. There is no difference between the symptoms and signs of children with intussusception at the time of recurrence. Paroxysmal crying is the most commonplace. Taking into account the intussusception, it will inevitably affect the blood supply to the intestine and will bring certain defects. Blood-reperfusion injury, so early

Table 1
Patient characteristics (n = 425).

Variable	Nonrecurrence (n)	Early recurrence (n)	<i>P</i> value
Age (y)			.002
<2	354	30	
≥ 2	21	7	
Gender			.851
Male	266	27	
Female	109	10	
Bloody stool			.037
Present	206	27	
Absent	169	10	
Vomiting			.684
Present	87	10	
Absent	288	27	
The duration of symptoms (h)			.363
<12	252	22	
≥ 12	123	15	
Season			.053
Spring	132	20	
Summer	82	4	
Autumn	89	10	
Winter	72	3	
Mass location			.027
Ascending colon	261	19	
Transverse colon	114	18	
enlarged lymph nodes			.511
Present	302	32	
Absent	70	5	
Intussusception history			.006
Present	39	10	
Absent	336	27	

Table 2
The expression of MCP-1 in nonrecurrence group and early recurrence group.

Group	cases	MCP-1 (pg/mL)	<i>t</i> -value	<i>P</i> value
Nonrecurrence	375	16.78 ± 10.29	9.657	0.000
Early recurrence	37	34.65 ± 14.58		

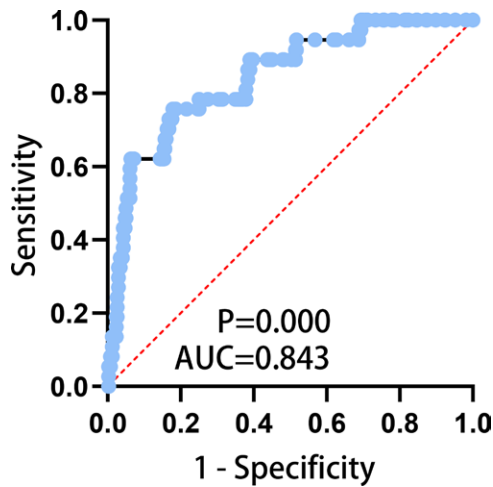


Figure 1. ROC analysis of MCP-1 for diagnosing short-term recurrence of intussusception in children. MCP-1 = monocyte chemoattractant protein-1, ROC = receiver operating curve.

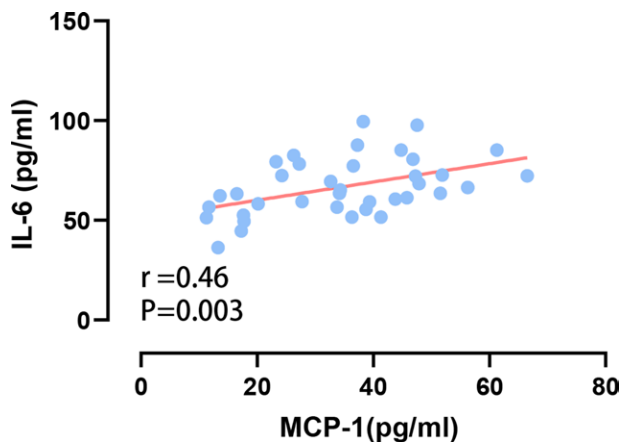


Figure 2. Correlation analysis between MCP-1 and IL-6. IL-6, interleukin-6, MCP-1 = monocyte chemoattractant protein-1.

detection of recurrence and shortening the time from onset of intussusception to treatment is of great significance.

As early as 1991, immunologists pointed out that the intestine is the largest lymphatic organ in the human body and is widely involved in local inflammatory immune responses.^[12] The occurrence of pediatric intussusception is closely connected with the immune status of the intestinal tract. Any change in the immune response of the intestine can affect the movement status of the intestinal tract in children. The mechanism is primarily reflected in the function of immune cells and inflammatory mediators on the smooth muscle of the intestine.^[13] MCP-1 is an important inflammatory mediator. It is a member of the CC family of chemokines. It is just a little molecule of a heparin-binding protein encoded by the MCP-1 gene, which can play a wide range of biological functions after binding to the CCR2 receptor.^[14] Studies have demonstrated that MCP-1 can recruit monocytes and lymphocytes, cause local white blood cell aggregation, and activate macrophages. Macrophages promote cell apoptosis through phagocytic cell debris and secretion of cytokines, thereby aggravating the inflammatory response.^[15] Our study found that in children with primary short-term relapse of intussusception, the expression of MCP-1 in the peripheral blood was significantly greater than that of non-relapsed children. Some scholars have pointed out that the occurrence of primary intussusception has a clear relationship with some inflammatory

Table 3

Logistic regression analysis of risk factors for early recurrence in children with primary intussusception.

Variables	OR	95% CI		P value
		Low	Up	
Age	1.059	1.012	1.109	.014
Bloody stool	1.363	0.567	3.278	.489
Mass location	0.397	0.175	0.904	.028
Intussusception history	4.820	1.803	12.881	.002
MCP-1	1.108	1.075	1.141	.000

mediators, such as IL-6. As an inflammatory mediator, IL-6 affects the contraction and relaxation of intestinal smooth muscle in primary intussusception. It can regulate the function of B cells, induce the shedding of mast cell particles, and increase the release of prostaglandins, then enhance the contraction of intestinal smooth muscle and induce intussusception.^[16,17] In this group of experiments, we found that in 37 relapsed children, the expression of MCP-1 increased, and there was a positive correlation with the expression of IL-6, so it is speculated that MCP-1 and IL-6 can interact and increase the contraction of the smooth muscle of the intestine leads to short-term recurrence of intussusception. And some scholars have found that in rheumatoid arthritis, urinary tract infection, chronic obstructive pulmonary disease, and many other diseases, the expression of MCP-1 and IL-6 are positively correlated, and can jointly enhance the inflammatory response.^[18-20] In pediatric primary intussusception, the specific mechanism of the relationship between the two still needs further research. The cost of screening MCP-1 and IL-6 in our hospital is about 10 US dollars, although this may increase the burden on patients, this screening can detect children who may relapse early, so early intervention will be exerted, and reduce the chance of short-term recurrence of intussusception, it will bring greater benefits to children.

We further analyzed ROC and found that MCP-1 has certain significance in predicting whether children with primary intussusception will relapse in a short period. Analysis of 412 children showed that the area under the curve was 0.843, and the best cut-off value was 23.24 ng/mL. Under this reference value, the sensitivity for predicting the recurrence of intussusception in children was 82.14% and the specificity was 75.67%. It is suggested that MCP-1 may be an important consideration affecting the recurrence of primary intussusception. In addition, the logistic regression results showed that the age of the child, the position of the cap, and the presence or absence of previous seizures are also factors that affect the short-term recurrence of primary intussusception. In a 2018 study in the United States, a total of 360 children were included, 32 of which had short-term relapses. It was of the view that children older than 2 years were the only short-term relapse factor. It was considered that children with intussusception over 2 years old were less; need longer diagnosis and treatment time, so it is easier to relapse.^[21] Although this is similar to our results, most scholars believe that the time from the onset of intussusception to the removal of the intussusception is not a factor that affects its recurrence. We are not supported by those children over 2 years of age who are prone to short-term relapse because of the need for a longer diagnosis. And the treatment time, we think that the function of the smooth muscle of the bowel in these older children may have not yet been fully developed. When encountering certain stimulating factors, they are the most likely to have contractile dysfunction, induce intestinal sleeves, and are more likely to relapse. There continues to be controversy as to whether the hedging position has an impact on short-term recurrence.^[22] Our results show that the hedging in the transverse colon is more prone to short-term recurrence,

which may demand a larger sample of studies to verify. Previous seizures are also a factor affecting short-term recurrence. Excluding secondary factors, in children with recurrent intussusception, we speculate that there may be a few functional disorders in the intestinal tract of this part of children, causing smooth muscle relaxation and contraction to be more susceptible to external factors. The influence of inflammatory factors, such as the stimulation of inflammatory factors, can easily lead to recurrence of intussusception. The peculiar reasons need to be further studied, and there are no reports in the literature.

Of course, this study also has some shortcomings. It is just a retrospective observational clinical study with a single center and a small sample. The role of MCP-1 in predicting the short-term recurrence of primary intussusception has still not been determined by a multi-center, large sample. Prospective research is also needed further verified in animal experiments. Even so, we first explored the clinical significance of MCP-1 in the short-term recurrence of primary intussusception, especially for children with further risk factors. It recommends observing closely, preferably in a hospital. Some scholars believe that short-term use of glucocorticoids or cyclooxygenase inhibitors can inhibit the inflammatory response and reduce the probability of short-term recurrence.^[2,3] We consider that it can be applied appropriately when there are multiple risk factors.

Author contributions

DSZ carried out the design and coordinated the study, and participated in most of the experiments. XFX, MZ, and TW coordinated and carried out all the experiments, and analysis of data and participated in manuscript preparation. All authors have read and approved the content of the manuscript.

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