

Inflammatory Markers in Children With Newly Diagnosed Inflammatory Bowel Disease

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Received: May 23, 2016

Revised: July 7, 2016

Accepted: July 9, 2016

Published online: April 21, 2017

abnormal tests. These patterns should be considered when investigating children with symptoms of possible IBD: one marker should not be considered in isolation.

Key words: Crohn disease; Children; Ulcerative colitis; Serum markers; Inflammation

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Day AS, Hamilton D, Leach ST, Lemberg DA. Inflammatory Markers in Children With Newly Diagnosed Inflammatory Bowel Disease. *Journal of Gastroenterology and Hepatology Research* 2017; 6(2): 2329-2332 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/1734>

INTRODUCTION

Up to one quarter of individuals with Inflammatory Bowel Disease (IBD) are diagnosed in childhood^[1,2]. Although symptoms such as abdominal pain, diarrhoea and weight loss are commonly seen, children may present with less specific symptoms, leading to delays in presentation and diagnosis^[2]. Importantly, diagnostic delay impacts adversely upon linear growth and pubertal development^[3,4].

The diagnosis of IBD relies upon clinical, laboratory, radiological, endoscopic and histological criteria. Prior to consideration of invasive investigations, such as endoscopy, less invasive tests can be utilised to indicate the presence of inflammation^[2]. Traditional indicators of inflammation have included serum markers, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), albumin and platelet count. These tests have the advantages of being cheap, straightforward and readily available. However, these tests are not specific for the gut, and may also have inadequate sensitivity.

We have previously evaluated CRP, ESR, albumin and platelet measurements in distinguishing between children shown to have IBD and a comparative group without organic disease^[5]. Receiver operator curve analyses showed that ESR results provided a superior area under the curve (91%) compared to the other markers. A recent multicentre North American study evaluated ESR, platelet count, albumin and haemoglobin levels in children at the time of diagnosis with IBD^[6]. ESR was most likely to be elevated in this group of children, whilst albumin levels were least helpful. The four markers were all

ABSTRACT

AIM: Various markers of inflammation are commonly utilised in the assessment of children with symptoms suggestive of Inflammatory Bowel Disease (IBD). The aim of this study was to outline the results of standard inflammatory markers in a large group of children at the time of diagnosis with IBD.

METHODS: The results of four standard inflammatory markers (ESR, albumin, platelet count and CRP) measured in a cohort of children diagnosed with IBD over a ten year period were reviewed retrospectively. Baseline demographic data, nutritional status (weight and height), disease type and disease location were also recorded.

RESULTS: Data was available for 206 children diagnosed with IBD: 146 were diagnosed with Crohn disease (CD), 30 with ulcerative colitis (UC) and 30 with IBD unclassified (IBDU). Children with CD had longer duration of symptoms, and weighed less with lower BMI than children in the other disease groups. Furthermore, albumin levels were lower and platelets counts higher in children with CD. All four of the tests were normal in 13% of children with CD and 36% of those with IBDU. Children with CD were more likely to have abnormalities in all four tests.

CONCLUSIONS: Children with CD were more likely to have abnormal systemic inflammatory markers and to have multiple

normal in around one fifth of children with mild CD and more than half the children with mild UC.

The objective of this study was to retrospectively ascertain the results of four standard tests in a group of children diagnosed with IBD and to delineate relationships between these markers and other key features at the time of diagnosis.

METHODS

Patients

The patient cohort comprised children diagnosed with IBD at Sydney Children's Hospital (SCH), Randwick, NSW, Australia, between the dates of January 1998 and July 2007. The diagnosis of IBD, and classification as Crohn disease (CD), ulcerative colitis (UC) or IBD-unclassified (IBDU), was based upon standard laboratory, radiological or endoscopic findings^[2,7]. All children had undergone upper gastrointestinal endoscopy and ileo-colonoscopy at diagnosis. The date of diagnosis was recorded as time of the definitive endoscopic assessment.

Data Collection

The SCH IBD Database was utilised to retrospectively review the required data. The database includes demographic data, disease type and location, racial origins, nutritional markers and standard laboratory results at the time of diagnosis with IBD. Patients were excluded if insufficient data were available at diagnosis. Following the extraction of required data from the database, the patient files of IBD patients were then reviewed and data confirmed or clarified.

Data management

Reference ranges for biological markers were CRP < 5 mg/L, ESR < 20 mm/hr, platelet count 150–450 × 10⁹/L and albumin 36–45 g/L. The levels of CRP, ESR and platelet count were considered as either normal or elevated whilst the results of albumin measurements were considered as normal or decreased. The total values for the four markers were also recorded. The location of disease for CD and UC was categorised using Montreal criteria^[8].

Weight, height and BMI were converted into Z scores and percentiles using EpiInfo (Centers for Disease Control and Prevention, Atlanta, GA, USA).

Statistical analysis

Data were analysed by ANOVA with Tukey post hoc test and presented as the mean (± standard deviation). Chi Square and Fisher's exact test were used to test categorical data with data displayed in contingency table form. GraphPad Prism version 6.00 for Windows (GraphPad Software, La Jolla California USA) was used for analyses. *P* value of < 0.05 was considered significant.

RESULTS

Patient characteristics and disease location

The data for 222 children were reviewed: 16 children were not included due to lack of adequate baseline data. Of the final study group of 206 children, 146 were diagnosed with CD (87 male), 30 with UC (16 male) and 30 labelled as IBDU (12 male) (Table 1). The mean ages and the gender ratios of the three groups were similar. The children with CD had a longer period of symptoms prior to diagnosis than those with UC (*p* = 0.018) (Table 1).

Just over half of the children with CD were found to have ileocolonic location (*n* = 77, 53%), whilst 51 had colonic and 16 had ileal disease. Upper gut involvement was seen 114 (78%) of the children

with CD, with two having isolated upper gut disease. Fifteen (10%) of the children had perianal disease at diagnosis. Twenty-five of the 30 children with UC had pan-colonic disease: the other five had left-sided disease (no children had isolated proctitis). Each of the children labelled as IBDU had pan-colonic changes.

Growth status at diagnosis

Nutritional information at diagnosis was available in 150 children (107 with CD, 21 with UC and 22 with IBDU). Overall these children had weight z score of -0.32 (1.26) and height z score of -0.03 (1.14). Overall BMI z scores were -0.45 (1.4). In addition, 21 (14%) children with CD were overweight (BMI centile > 85%) or obese (BMI centile > 95%). Thirteen of these children were diagnosed with CD, 2 UC and 6 IBDU.

Children with CD had lower weight z scores at diagnosis compared to the other groups combined (*p* = 0.006) (Table 1). There were no differences between the groups for height z scores at diagnosis. BMI z scores were lower in the CD group (ANOVA; *p* = 0.03).

Standard Inflammatory markers in CD and UC/IBDU

The measured ESR and CRP values were not different between the three groups (*p* > 0.05) (Table 2). Albumin levels were lower and platelet levels higher in the CD group than the combined groups (*p* = 0.02 and 0.005 respectively).

When considered as normal or abnormal, ESR, CRP, albumin and platelet results were more frequently abnormal in the CD group (Table 2). When the number of normal or abnormal tests was determined within each group, 19 (13%) children with CD were found to have four normal tests whilst 52 (36%) had four abnormal tests (Table 3). The number of children with four normal tests was lower in the CD group than the IBDU group (13% vs 36%; *p* = 0.01). Eleven of the 27 children with UC had none or one abnormal test. In addition, the number of children with four abnormal tests was greater in the CD group (*p* = 0.03).

In the CD cohort ESR and CRP values were discordant on 21 occasions: in 16 instances ESR was elevated with normal CRP, whilst a high CRP and normal ESR was seen in five children. In the group of children with UC and IBDU, high ESR and normal CRP was seen in 16 children, with one instance of isolated elevation of CRP.

Serum inflammatory markers and disease location

ESR and platelet counts did not differ according to disease location

Table 1 Background characteristics of 206 children diagnosed with Inflammatory Bowel Disease.

	CD	UC	IBDU	<i>p</i> values
N	146	30	30	
Age (years)				
Mean (SD)	9.9 (4.1)	10 (4.1)	8.4 (4.3)	NS
Range	0.6-17	Feb-16	0.75-15	NS
Gender (M)	87 (60%)	16	12	NS
Symptoms (wks)	49.4 (57.1)*	23.8 (26.2)	32.3 (29.8)	<0.05
Weight	-0.496 (1.25)*	0.039 (1.13)	0.192 (1.31)	0.006
Height	-0.116 (1.13)	0.333 (1.29)	0.025 (1.01)	NS
BMI	-0.656 (1.48)*	-0.211 (1.17)	0.251 (1.13)	0.03

The children with Crohn disease (CD) had longer period of symptoms prior to diagnosis, weighed less and had lower BMI than the other groups (ANOVA). Post-hoc *t* tests showed that the CD group differed from the UC group (as indicated by *). Growth parameters expressed as z scores (SD). UC = ulcerative colitis, IBDU = Inflammatory bowel disease unclassified, CD = Crohn disease, NS = Not Significant.

in children with CD (data not shown). Higher CRP values and lower albumin levels were seen in the group with ileal or ileocolonic involvement, compared to those with isolated colonic disease (L2) ($p = 0.03$ for both) (Table 4). The same relationship was seen when L2 was compared to L1 and L3 combined ($p = 0.02$ for both markers).

There were no differences between ESR, CRP and platelet counts according to the presence or absence of upper gut involvement in children with CD (data not shown). However, the children with upper gut involvement had lower albumin levels than those with disease in the ileum or colon only (33.1 ± 6.6 g/L vs 36.6 ± 6 g/L; $p = 0.01$).

There were no relationships between disease location and any of the four inflammatory markers for the children with UC or those with IBDU (data not shown).

DISCUSSION

This retrospective study demonstrates the variability of standard serum-based inflammatory markers in children at the time of diagnosis of IBD. ESR was the most useful of the four indicators assessed, being least commonly normal in these children. Generally, the markers were more likely to be altered in individuals with CD than those with UC or IBDU. However, these serum markers were not able to differentiate between CD and UC. Albumin levels were lower in children with ileal involvement or those with upper gut involvement, but were not able to distinguish between differences in disease location in the setting of CD.

Traditionally, serum-based markers are utilised as initial investigations in a child presenting with symptoms suggestive of possible IBD. ESR, CRP, platelet count and albumin testing are all easily available with rapid determination of results within the same day. Each of these markers, however, may be altered consequent to various other processes, such as a local or systemic bacterial infection. Consequently, these markers lack specificity for gut inflammation.

Other serum-based inflammatory markers are also available and may provide additional information^[9,10]. Orosomucoid, an acute phase protein, is available in some laboratories^[11]. Ferritin, a measure of iron stores, is also an acute phase protein, increasing with CRP in the setting of acute infection or inflammation^[12]. Orosomucoid was not routinely measured in the laboratory of the current study, whilst ferritin results were not reviewed in the current study.

Stool-based markers may also assist in the determination of possible gut inflammation in individuals with undifferentiated symptoms^[13,14]. Whilst identification of faecal white cells or measurement of faecal α -1-antitrypsin can be utilised, neither of these tests provides adequate sensitivity or specificity for gut inflammation^[15]. Many studies have focused upon the development and assessment of specific faecal inflammatory markers as non-invasive tools. Measurement of faecal calprotectin (FC) has been shown to provide high specificity and sensitivity for gut inflammation^[13]. FC measurements are now available routinely in many countries, and may provide helpful information in the primary care or secondary care settings to direct the triage of patients requiring endoscopic assessment. Other faecal markers include S100A12, lactoferrin and osteoprotegerin^[15,16]. Faecal assays were not available in the current study.

Several recent reports have evaluated serum-based inflammatory markers in the context of children diagnosed with IBD. Mack *et al*^[6] reported the results of ESR, albumin, and platelet counts along with haemoglobin levels in a large group of children across a number of North American centres at the time of diagnosis with CD. CRP was

Table 2 Results of four inflammatory markers in children at the time of diagnosis of Inflammatory Bowel Disease.

	CD	UC	IBDU	P values
ESR (mm/hr)				
Mean (SD)	31.4 (23.5)	29.4 (27.5)	23.1 (23.6)	NS
Abnormal (%)	60	55.5	35.7	$p = 0.002$
CRP				
Mean (SD)	26.1 (38.6)	19.1 (44.5)	13.6 (33.8)	NS
Abnormal (%)	66.9	48	42.3	$p = 0.0002$
Albumin (g/L)				
Mean (SD)	33.8 (6.6)	36.6 (5.8)	36.7 (6.6)	$p = 0.02$
Abnormal (%)	59.1	42.8	33	$p < 0.001$
Platelets				
Mean (SD)	439 (138)	415 (75)	355 (115)	$p = 0.005$
Abnormal (%)	68.6	22	41.6	$p < 0.001$

ESR, CRP, Albumin and platelets results were available for 206 children at the time of diagnosis of Inflammatory Bowel Disease. Mean values with standard deviations were calculated for each marker (and compared using ANOVA). In addition, the percentage of abnormal results for each marker was also derived (and compared using Chi squared tests). CD= Crohn disease, UC = ulcerative colitis, IBDU = inflammatory bowel disease unclassified (IBDU), NS = Not Significant.

Table 3 Numbers of abnormal tests in children with Inflammatory Bowel Disease.

	Number of Abnormal tests				
	0	1	2	3	4
CD ($n = 144$)	19	25	26	24	52
UC ($n = 27$)	4	7	5	3	8
IBDU ($n = 28$)	10	5	8	2	3

Measurements of ESR, CRP, Albumin and platelet count were reviewed in children at time of diagnosis of Crohn disease (CD), ulcerative colitis (UC) or IBD Unclassified (IBDU). The numbers of abnormal test results in each disease grouping was assessed. Children with CD were more likely to have four abnormal test results ($p = 0.03$).

Table 4 Relationship between inflammatory markers and disease location in 146 children with Crohn disease.

	L1	L2	L3	ANOVA
ESR	34.3 (14.7)	27.1 (22.9)	33.9 (25.5)	NS
CRP	42.1 (50.7)	15.9 (27.7)	29.7 (41.1)	0.03
Albumin	30.9 (6.5)	35.5 (6)	33.2 (6.8)	0.03
Platelets	434 (137)	443.4 (158)	436.9 (127)	NS

Higher CRP and lower albumin values were seen in children with any ileal involvement compared to isolated colonic disease. CRP values were higher in the combined L1 and L3 group compared to the L2 group ($p = 0.02$). Similarly, albumin levels were lower in the combined L1 and L3 group compared to the L2 group ($p = 0.02$). Data presented as mean values plus standard deviations. NS= Not significant.

not evaluated in this report. In this group of 526 children, the ESR was the least likely to be normal: ESR was abnormal in three-quarters of the children. Albumin, in contrast, was abnormal in just 40% of these children. Similar patterns were observed in the current study.

A further North American study specifically evaluated standard serum markers (ESR, CRP, albumin, platelets and haemoglobin) in a group of 258 children with IBD and 197 control children without IBD^[17]. Similar to the earlier study, ESR was abnormal in 75% and albumin was lowered in 37% of the children with IBD. CRP was abnormal in 76%. Just 14% of the children with IBD had a normal CRP and ESR, contrasting to 79% of the control group. Consistent with the current study, there was discordance between ESR and CRP results. Overall, the authors concluded that the addition of CRP to

the testing panel identified most of the children with IBD, with the exception of those with mild UC^[17].

Similar conclusions were drawn by the authors of an evaluation of CRP and ESR in 451 children with UC, drawn from several distinct cohorts^[18]. CRP and ESR were both normal in 34% of those with mild disease activity, and 5-10% of those with moderate-severe activity. Discordance between CRP and ESR results was noted in up to 38% of the children. Longitudinal analysis in a subset of these children demonstrated that when either the CRP or ESR is helpful in a particular patient initially, this marker tends to remain helpful over time^[18].

At present, in the assessment of a child with gastrointestinal symptoms, a broad assessment of serum inflammatory markers would be most reasonable, with inclusion of ESR, CRP, albumin and platelet count as a panel. Reliance upon just one marker may lead to individuals with IBD not being identified at this time. However, the validity of this recommendation does require prospective assessment of children presenting with gastrointestinal symptoms.

This report is limited in part by the nature of the retrospective study design, with incomplete data limiting more detailed analyses. Nutritional information at diagnosis was not available in all subjects. In addition, an assessment of disease activity at diagnosis was not available in this group, which prevented an assessment of the relationship between the serum markers and disease severity scores. The current data was not controlled for patients without IBD, meaning that sensitivities and specificities for each marker could not be estimated. However, the data included a large cohort of children who had completed a consistent diagnostic workup at a single tertiary unit. The data is likely representative of other children diagnosed with IBD in Australasia.

In conclusion, these data indicate variability in serum inflammatory markers in children at the time of diagnosis of IBD, with these tests more frequently abnormal in CD than in UC. These data support the use of a series of serum inflammatory markers, rather than reliance upon one or even two specific tests in children with possible IBD. However, this retrospective study was not able to evaluate the performance of these markers in comparison to stool based inflammatory markers.

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Peer reviewer: Ole Haagen Nielsen.