

Effect of inflammatory attacks in the classical type hyper-IgD syndrome on immunoglobulin D, cholesterol and parameters of the acute phase response

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Abstract. Simon A, Bijzet J, Voorbij HAM, Mantovani A, van der Meer JWM, Drenth JPH (University Medical Centre St. Radboud, Nijmegen; University Hospital Groningen, Groningen; University Medical Centre Utrecht, Utrecht, The Netherlands; Mario Negri Institute for Pharmacological Research, Milan, Italy; and National Institutes of Health, Bethesda, MD, USA). Effect of inflammatory attacks in the classical type hyper-IgD syndrome on immunoglobulin D, cholesterol and parameters of the acute phase response. *J Intern Med* 2004; **256**: 247–253.

Background. Classical type hyper-immunoglobulin D (IgD) syndrome (HIDS) is an hereditary auto-inflammatory disorder, characterized by recurrent episodes of fever, lymphadenopathy, abdominal distress and a high serum concentration of IgD. It is caused by mevalonate kinase deficiency.

Objective. To further characterize the acute phase response during fever attacks in HIDS in order to improve diagnosis.

Subjects. Twenty-two mevalonate kinase-deficient HIDS patients.

Methods. Blood samples were drawn during and in between febrile attacks, and concentrations of C-reactive protein (CRP), ferritin, procalcitonin,

pentraxin 3, IgD and cholesterol in several lipoprotein fractions were determined.

Results. The marked acute phase response at the time of a fever attack in classical type HIDS is reflected by a rise in CRP accompanied by a moderate but statistically significant rise in procalcitonin and pentraxin 3. In only two of 22 patients, procalcitonin concentration rose above 2 ng mL^{-1} during fever attack, compatible with the noninfectious nature of these attacks. Ferritin does not reach the high concentrations found in adult-onset Still's disease. Despite the defect in mevalonate kinase, a component of cholesterol metabolism, serum cholesterol did not change during attacks. IgD concentration is elevated regardless of disease activity, although there is appreciable variation during life. Its role in HIDS remains unclear.

Conclusion. The combination of high CRP concentration plus procalcitonin concentration $< 2 \text{ ng mL}^{-1}$ in a symptomatic HIDS patient might indicate a febrile attack without (bacterial) infection; this observation warrants further investigation for its usefulness as a marker in clinical practice.

Keywords: acute phase response, ferritin, hyper-IgD syndrome, immunoglobulin D, pentraxin-3, procalcitonin.

Introduction

The hyper-immunoglobulinaemia D and periodic fever syndrome (HIDS) is a rare disorder which

causes life-long recurrent episodes of fever and inflammation [1]. Clinically, these episodes may be accompanied by abdominal distress, arthralgia, headache, lymphadenopathy, skin rash and

aphthous ulcers [2]. The inflammatory attack lasts about 4–6 days followed by a spontaneous remission, only to recur after a symptom-free period of 4–6 weeks. Attacks can be triggered by minor trauma, vaccinations and physical or emotional stress, but often come unexpectedly. Laboratory examination at the time of attacks reveals a vigorous acute phase response with leucocytosis, raised sedimentation rate and high serum concentrations of C-reactive protein and pro-inflammatory cytokines such as interferon- γ , tumour necrosis factor- α , and interleukin-6 [3, 4]. Almost all patients have an elevated polyclonal immunoglobulin D (IgD) and IgA concentration. Previously, we have distinguished classical type HIDS and variant type HIDS [5]. Whilst in variant type HIDS the nature of the underlying defect is unclear, classical type HIDS is caused by mutations in the gene encoding for mevalonate kinase, an enzyme that is part of the isoprenoid pathway. The genetic mutations cause a diminished enzyme activity of mevalonate kinase, and during a fever attack its substrate, mevalonic acid, will accumulate in body fluids and be excreted in the urine. End products of this pathway include cholesterol, dolichol and ubiquinone, and the isoprenoid pathway is also essential for the isoprenylation of proteins, a modification important for membrane-bound proteins. The link between the defective isoprenoid metabolism and the inflammatory phenotype of HIDS remains to be resolved.

The main aim of this study was to further define the acute phase response in the inflammatory attacks in classical HIDS patients, actuated by two considerations. In the first place, we sought to discriminate between (serious bacterial) infection and noninfectious inflammation of a HIDS attack. Such a differentiation is needed in clinical practice as the inflammatory episodes in HIDS, with high fever and often severe abdominal distress, can pose a serious diagnostic dilemma and frequently lead to unnecessary use of antibiotics or even avoidable surgical procedures. This prompted us to consider two recently characterized members of the family of acute phase proteins as a biological marker: procalcitonin (PCT) and pentraxin 3 (PTX3) [6–9]. Furthermore, we wanted to test serum concentrations of IgD, ferritin and cholesterol in HIDS patients with and without fever, which might be of help in differential diagnosis.

Patients and methods

Patients

We included in this study 22 (12 males and 10 females) Dutch patients with classical type HIDS. All patients suffered from typical recurrent fever episodes, shared elevated serum concentrations of IgD and carried mevalonate kinase gene mutations. The main patient characteristics are listed in Table 1. Sampling of plasma and serum was performed at two time-points, during fever attack and during remission. Our definition of a fever attack for the present study consisted of (i) raised body temperature (≥ 38 °C), (ii) typical symptoms and signs of HIDS as mentioned earlier, and (iii) no clinical indications for the presence of infection. Remission was defined as the absence of symptoms for at least 1 month. No medication was allowed during the study period. Close follow-up of the patients did exclude bacterial and/or viral infections during the course of the investigation. All patients recovered from the fever episode spontaneously without the use of antibiotics or antiviral medication. The ethical committee of our institution approved the study protocol, and all patients gave informed consent. In order to delineate the course of IgD during life, we took historical IgD values from patient records from 17 classical-type HIDS patients, which were available to us through the Nijmegen HIDS registry [2].

Serum and plasma determinations

Determination of each protein was performed in one assay for all samples. CRP concentrations were measured in duplicate by a polyclonal antibody enzyme-linked immunosorbent assay (ELISA) as previously reported (normal reference < 2.7 mg L⁻¹) [10]. Concentration of procalcitonin was determined by chemiluminescent solid phase double antibody immunoluminometric assay (LUMitest; BRAHMS Diagnostica GmbH, Berlin, Germany). Two specific monoclonal antibodies form a sandwich by binding the two major polypeptide chains of procalcitonin (catalcalcin and calcitonin); the second antibody carries a luminescent tracer. The light emission triggered by oxidation in the presence of hydrogen peroxide can be measured by luminometer (detection limit 0.05 ng mL⁻¹, normal

Table 1 Patient characteristics

Patient no.	Sex	Age (years)	Onset (months)	MVK genotype	Fever	Lymphadenopathy	Abdominal pain	Arthralgia	Skin lesions
1	F	17	8	V377I/I268T	+	+	+	-	-
2	M	18	4	P167L/I268T	+	+	+	+	+
3	M	22	0	V377I/I268T	+	+	+	+	+
4	M	23	3	V377I/H20P	+	+	+	+	+
5	F	26	2	V377I/H20P	+	+	+	-	+
6	M	30	3	V377I/H20P	+	+	+	+	+
7	M	31	18	P167L/I268T	+	+	+	+	+
8	F	34	0	V377I/unknown ^a	+	+	+	+	-
9	F	34	12	P167L/G202R	+	+	+	+	+
10	M	37	96	V377I/unknown ^a	+	+	+	+	+
11	F	37	0	V377I/I268T	+	+	+	+	+
12	F	38	3	V377I/V377I	+	+	+	+	+
13	M	40	24	V377I/deletion	+	+	+	+	+
14	M	41	48	V377I/unknown ^a	+	+	-	+	+
15	F	42	12	V377I/deletion	+	+	+	+	+
16	M	45	0	V377I/W62X	+	+	+	+	+
17	M	46	0	V377I/W62X	+	+	+	+	+
18	F	52	?	V377I/G309S	+	+	-	-	+
19	F	54	0	V377I/deletion	+	+	-	+	+
20	M	54	3	V377I/I268T	+	+	+	+	+
21	F	54	12	V377I/I268T	+	+	-	-	-
22	M	58	48	V377I/H20P	+	+	-	+	+

^aIn three patients where only one mutation in the MVK gene could be identified, the diagnosis of classical type HIDS was confirmed by the detection of increased urinary mevalonic acid excretion during inflammatory attack (patient 8) or decreased mevalonate kinase enzyme activity (patients 10 and 14).

reference $<0.5 \text{ ng mL}^{-1}$, reference limit used in case of bacterial infection $<2 \text{ ng mL}^{-1}$) [11, 12].

Plasma concentration of pentraxin 3 was measured by ELISA, based on the PTX3-specific monoclonal antibody MNB4 and biotinylated rabbit PTX3-specific polyclonal IgG (normal reference $<2 \text{ ng mL}^{-1}$) [13, 14].

The procedure for the ELISA for measurement of IgD has been published earlier, using rabbit anti-human IgD (Dako, Copenhagen, Denmark) as the primary antibody [15]. The lower limit of detection of this ELISA was 1 IU mL^{-1} (1.4 mg L^{-1}), normal reference $<100 \text{ IU mL}^{-1}$.

Concentrations of cholesterol were measured on the Hitachi 747 analyzer with enzymatic, commercially available reagents (Boehringer-Mannheim, Mannheim, Germany) (normal reference $4.7\text{--}6.5 \text{ mmol L}^{-1}$). HDL cholesterol was measured in the supernatant after precipitation with PEG 6000 on the Hitachi 747 analyzer using commercially available reagents [16]. LDL cholesterol was calculated by the Friedewald formula (normal reference limit $<4.7 \text{ mmol L}^{-1}$) [17].

Ferritin was measured on the Immulite 1 (DPC, Los Angeles, CA, USA) using beads coated with monoclonal anti-ferritin and an alkaline phosphatase polyclonal conjugate (normal reference limit premenopausal women $80 \text{ } \mu\text{g L}^{-1}$, men and postmenopausal women $280 \text{ } \mu\text{g L}^{-1}$).

Statistical analysis

Statistical analysis was performed using GraphPad Prism version 4 for Windows (GraphPad Software, San Diego, CA, USA; <http://www.graphpad.com>). The paired nonparametric Wilcoxon signed rank test was used for statistical comparison of concentrations during remission and during fever attack. Correlation coefficients were calculated with the Spearman correlation test. Data are given as median (range) unless otherwise stated.

Results

During a fever attack, serum concentrations of CRP are invariably and significantly elevated to a median

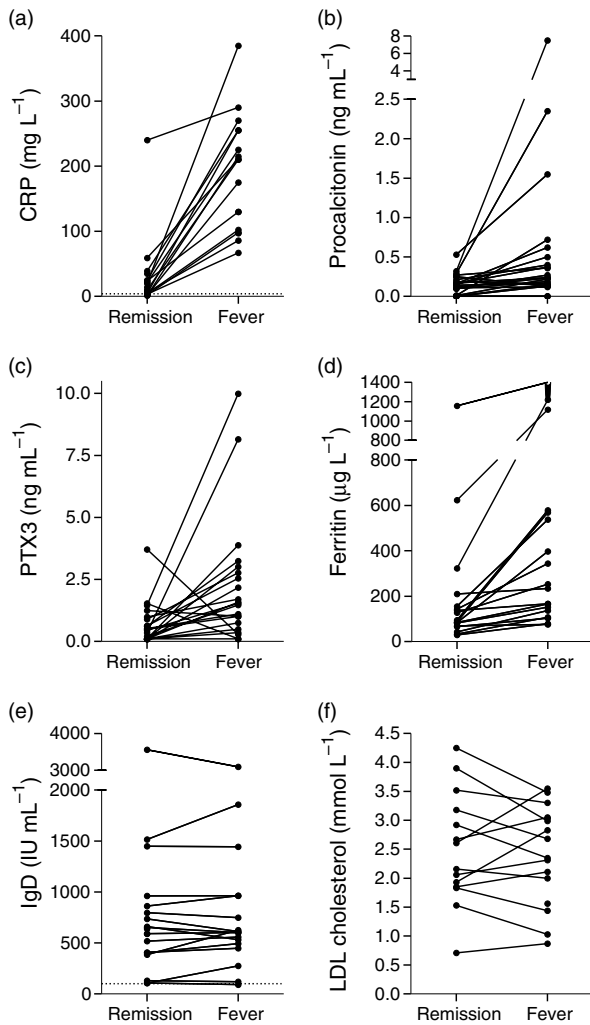


Fig. 1 The acute phase response in the fever attack of hyperimmunoglobulin D syndrome (HIDS). (a) serum concentration of C-reactive protein (CRP); (b) procalcitonin; (c) pentraxin-3; (d) ferritin; (e) immunoglobulin D; and (f) LDL cholesterol.

of 210 mg L⁻¹ (range 67–385 mg L⁻¹, *P* < 0.0001; Fig. 1a). During a period of remission when the patient is without any symptoms, CRP concentrations are significantly lower, although often (83% of cases) still elevated above normal (12 mg L⁻¹; range 1.3–240 mg L⁻¹).

At the time of fever episodes, most patients showed a limited, albeit statistically significant, rise in serum procalcitonin concentration (Fig. 1b; median 0.15 vs. 0.24 µg L⁻¹, *P* = 0.0005). A clinically significant increase above the reference limit of 2 ng mL⁻¹ used for bacterial infection was seen in only two patients. Procalcitonin concentra-

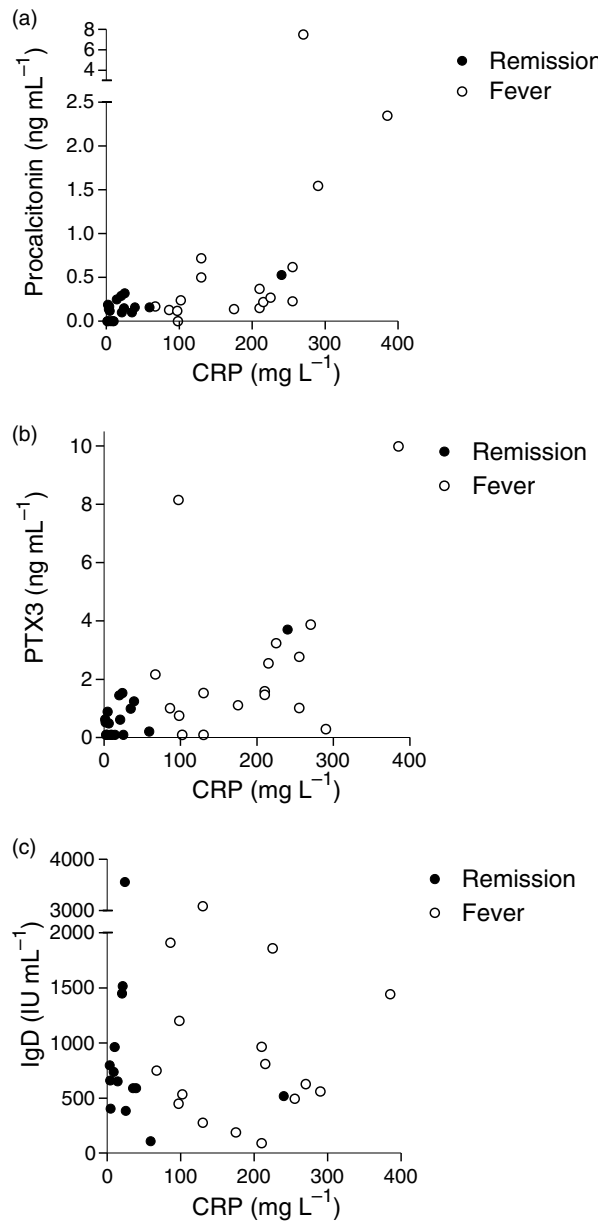


Fig. 2 Concentration of (a) procalcitonin, (b) pentraxin-3 and (c) immunoglobulin D versus serum concentration of C-reactive protein (CRP), demonstrating the absence of correlation except in the case of the procalcitonin versus CRP concentration during fever attack.

tions during fever attacks correlated with CRP concentrations (Fig. 2a, Spearman *r* = 0.71, *P* = 0.0013). PTX3 concentration (Fig. 1c) increased during fever in the majority of patients (median 0.45 vs. 1.53 ng mL⁻¹, *P* = 0.002), with a concentration >2 ng mL⁻¹ in eight of 21 patients. However, a correlation between CRP and PTX3

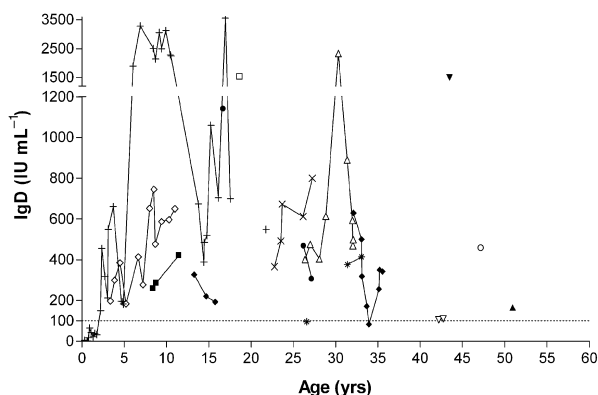


Fig. 3 Serum IgD concentration in 17 hyper-immunoglobulin D syndrome (HIDS) patients. Each symbol represents a separate patient, some of whom have been followed for several years. There is wide intra- and inter-individual variation.

was absent, also in the samples taken during fever attack (Fig. 2b).

Serum ferritin concentration increased in 61% of the patients during a fever episode, up to a maximum of $1398 \mu\text{g L}^{-1}$ ($P = 0.0002$, Fig. 1d). There was no indication for the presence of haemochromatosis in any of the patients, as ferritin values dropped to below $300 \mu\text{g L}^{-1}$ between attacks and the iron saturation as determined with transferrin saturation or unsaturated iron-binding capacity was below 45% (data not shown).

Immunoglobulin D (IgD) serum concentrations were elevated, in most patients to at least five times the upper level of normal. No difference was found in samples taken during remission or during a fever attack [median 639 IU mL^{-1} (range $108\text{--}3560 \text{ IU mL}^{-1}$) vs. 603 IU mL^{-1} (range $92\text{--}3090 \text{ IU mL}^{-1}$)] (Fig. 1e). There was no correlation between IgD and CRP values, either during attacks or during remission (Fig. 2c). Intraindividual IgD concentrations determined over a period of years show great variation (Fig. 3). All HIDS patients had normal to low-normal serum cholesterol concentrations during remission; this was true for total (mean $3.7 \text{ mmol L}^{-1} \pm 1.1 \text{ SD}$), LDL (mean $2.5 \text{ mmol L}^{-1} \pm 0.9 \text{ SD}$) and HDL cholesterol (mean $0.75 \text{ mmol L}^{-1} \pm 0.3 \text{ SD}$). No changes to any of these concentrations occurred during a fever attack (Fig. 1f).

Discussion

These results demonstrate the intense acute phase response during the fever episode of classical type

HIDS, and provide information on pathophysiological mechanisms. The acute phase response in HIDS is best defined by the sharp rise in serum concentrations of CRP (Fig. 1a). This response is similar to that described in patients with familial Mediterranean fever (FMF), although generally the acute phase response is more intense and more prolonged than in FMF [18–21].

Our main objective was to find a biological marker that discriminates between the noninfectious inflammation of a fever attack of HIDS and (bacterial) infection. To this end, we examined the acute phase proteins procalcitonin and PTX3. Both proteins showed a statistically significant rise during fever attacks, although only procalcitonin concentration during fever showed a significant correlation with CRP concentration. Specifically, procalcitonin values rose above the threshold of 2 ng mL^{-1} , used as reference limit for bacterial infection, only in two of 22 patients. This is similar to the findings in systemic autoimmune disease [7]. This suggests that the combination of a high serum CRP and procalcitonin concentration below 2 ng mL^{-1} may be used to distinguish an inflammatory attack of HIDS from an intercurrent bacterial infection. The sensitivity and specificity of this combination of markers needs to be determined in future studies. The specific cytokine profile in HIDS might account for the limited increase in PTX3 concentration as this acute phase protein is induced by interleukin-1 (and not by interleukin-6), whilst in HIDS interleukin-6 is far more upregulated than interleukin-1 [3, 8].

The cause of elevated IgD concentrations in the majority of HIDS patients, which prompted the name of this syndrome [22] is still an enigma. In children, fever attacks may precede the rise in serum IgD for several years [23]. In addition, some HIDS patients, despite having a severe phenotype, never develop high IgD [24], whilst a modest increase in IgD may be found in other hereditary autoinflammatory syndromes. On the contrary, isolated IgD elicits an inflammatory response in isolated mononuclear cells [15]. If the IgD elevation is a consequence of the inflammatory phenotype, it might be anticipated that its concentration varies with the attacks. In our study, serum IgD concentrations were continuously high, irrespective of inflammatory state and/or CRP concentration. In addition, serum IgD concentrations vary greatly during life

(Fig. 3), without correlation with clinical symptoms or frequency of attacks. These are further arguments to label the high IgD as an epiphenomenon rather than central to the pathogenesis. These data also indicate that the timing of IgD sampling for diagnostic purposes is irrelevant.

In our patients, we found relatively low serum LDL and HDL cholesterol concentrations during remission, but no further decrease with inflammatory attacks. This contrasts with the expected decrease in HDL cholesterol during inflammation as has been described for numerous inflammatory disorders [25–27], and this might be related to the enzyme defect of mevalonate kinase in HIDS.

Despite an elevated ferritin concentration during fever attack in 61% of HIDS patients, none of the patients showed the extremely high ferritin concentrations (>3000 ng mL⁻¹) found in adult-onset Still's disease [28–30], an inflammatory disorder with unknown aetiology, characterized by spiking fever, arthritis, evanescent rash and onset in adulthood [31].

In conclusion, the fever attack in HIDS is characterized by a strong rise in CRP concentration in all patients. Other acute phase proteins, such as pentraxin-3 and procalcitonin, showed an increase in some, but not all, patients. Specifically, this study suggests that in classical type HIDS a combination of high CRP concentration with procalcitonin below 2 ng mL⁻¹ can be used as an indication that a febrile attack is not due to intercurrent bacterial infection, which can reduce unnecessary use of antibiotic therapy. The same might be true for PTX3 when its limit is set higher, although this remains more speculative as less is known about the right cut-off point. The concentration of IgD, which is high in HIDS, is not influenced by the inflammatory episodes.

Conflict of interest statement

No conflict of interest was declared.

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