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Long-term follow-up, clinical features, and quality of life in a series of 103 patients with hyperimmunoglobulinemia D syndrome

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Abstract: The hyperimmunoglobulinemia D and periodic fever syndrome (HIDS), one of the autoinflammatory syndromes, is caused by mutations in the gene coding for mevalonate kinase (MVK). We conducted the current study to assess the genetic, laboratory, and clinical features as well as the complications and course of disease in patients with genetically confirmed HIDS. In addition, we studied the quality of life and course of life in a selection of patients. Follow-up data were obtained by a questionnaire sent to all physicians of patients in the International HIDS Database. In addition, we assessed the course of life and quality of life in Dutch patients aged >16 years using validated quality of life instruments.

Data were obtained from 103 patients from 18 different countries. The median age of first attack was 6 months (range, 0–120 mo), with a median period of 9.9 years from onset of disease to diagnosis. The most frequent symptoms that accompanied attacks of fever were lymphadenopathy, abdominal pain, arthralgia, diarrhea, vomiting, skin lesions, and aphthous ulcers. Amyloidosis was a severe but infrequent complication (2.9%). The median serum IgD level was 400 U/mL. IgD levels were normal in 22% of patients. The 4 most prevalent mutations (V377I, I268T, H20P/N, P167L) accounted for 71.5% of mutations found. The frequency of attacks decreased with the patient's increasing age, although 50% of patients over the age of 20 years still had 6 or more attacks per year. Many drugs have been tried in HIDS. Some patients responded to high-dose prednisone (24.4% response). Anakinra and etanercept can also be effective (33.3% response). Quality of life was determined in a subgroup of patients (n = 28). Social functioning, general health perception, and vitality were significantly lower in patients with HIDS than in controls, as were autonomy and social development. In addition, HIDS had an adverse impact on educational achievements and employment status. In conclusion, HIDS is an early-onset disease that is accompanied by an array of inflammatory symptoms. Although the frequency of attacks decreases during the patient's life, many patients continue to have frequent attacks. HIDS impairs several aspects of quality of life.

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Abbreviations: FMF = familial Mediterranean fever, HIDS = hyperimmunoglobulinemia D and periodic fever syndrome, MKD = mevalonate kinase deficiency, MVA = mevalonic aciduria, MVK = mevalonate kinase, RAND-36 = RAND-36 Health Survey, TAAQoL = TNOAZL Adult Quality of Life questionnaire, TRAPS = tumor necrosis factor-1 receptor-associated periodic syndrome.

INTRODUCTION

The hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) is one of the autoinflammatory fever syndromes. The autoinflammatory syndromes form a group of hereditary disorders characterized by lifelong recurrent inflammatory attacks, with fever as the most prominent symptom, usually accompanied by other phenomena such as arthritis, abdominal pain, diarrhea, lymphadenopathy, and skin lesions[14]. Inflammatory attacks are invariably associated with a vigorous acute-phase response and strongly elevated C-reactive protein and serum amyloid A[37]. The autoinflammatory syndromes include at least 6 different inherited disorders. They can be distinguished based on mode of inheritance and genetic basis. Familial Mediterranean fever (FMF), and HIDS are autosomal recessively inherited. On the other hand, tumor necrosis factor-1 receptor-associated periodic syndrome (TRAPS), and the cryopyrin-associated periodic syndromes (CAPS)[38] are dominantly inherited. Research into the autoinflammatory disorders has been boosted by the elucidation of the molecular origins. HIDS is caused by mutations in the gene that encodes mevalonate kinase (MVK)[13,19]. This is an enzyme in the isoprenoid pathway in which cholesterol is produced, in addition to a number of nonsterol isoprenoids. Isoprenoids are essential compounds in diverse cellular functions and include farnesyl, geranyl, and ubiquinone[20]. Mutations in MVK lead to 2 distinct syndromes: HIDS as a mild

phenotype, and mevalonic aciduria (MVA) as a more severe phenotype; collectively they are sometimes designated "mevalonate kinase deficiency" (or MKD). Although the incriminating gene was discovered in 1999, the exact mechanism of inflammation in HIDS has not been elucidated. An increased production of interleukin-1β by mononuclear cells has been suggested as a central mechanism in the inflammatory phenotype of HIDS[12,16]. Recently, it has been shown that a deficiency in geranylgeranyl, one of the isoprenoids, leads to increased production of interleukin-1β by human mononuclear cells, providing further evidence for a central role of interleukin-1β in the pathogenesis of HIDS[22,24]. Also, it has been shown that lymphocytes from HIDS patients show a defective apoptosis. This may lead to an unbridled inflammatory response after a minor stimulus, as an explanation for the inflammatory phenotype of HIDS[4].

The first patients with HIDS were described in 1984[39]. In 1994, the International HIDS Study Group was established to collect data on patients with this rare disease. In an article in this journal 14 years ago, before the discovery of the causative gene mutations, we presented preliminary data on 50 patients who, on clinical grounds, were classified as having HIDS[11]. Apart from the fact that our previous study necessarily included patients diagnosed based on only clinical criteria, it also left a number of questions unanswered. The prevalence of amyloidosis or the development of other complications was unknown, as was the possible effect on mortality. Further, the general clinical impression was that the frequency of attacks abates with time, but that has never been substantiated. Also, the effect of this syndrome on several dimensions of the quality of life has not been studied previously.

We conducted the current study to characterize a large international cohort of patients with mutation-positive HIDS in detail, including assessing the genetic, laboratory, and clinical features, but most especially assessing the prevalence of complications, survival, and progression of disease. In addition, we studied the quality of life and course of life in a selection of patients.

PATIENTS AND METHODS

In the International HIDS Database (www.hids.net), we collect data about patients with suspected and confirmed HIDS. Data are submitted by the patient's physician. With the submission of a new patient to the registry, physicians are asked about clinical features, inflammatory markers, serum immunoglobulin concentrations, and results of mutational analysis. This database does not contain data on patients with the more severe phenotype of MVA. Although somewhat arbitrary, we considered patients with any of the following as having MVA: severe psychomotor retardation, progressive cerebellar ataxia, typical dysmorphic features, and progressive visual impairment[18]. A total of 244 patients was submitted up to January 2007. In 47 patients, genetic testing did not reveal mutations in MVK. In 71 patients, genetic testing was not performed or data about testing were unavailable. Some genetic laboratories tested only for the most common mutations. A total of 126 patients with mutation-positive HIDS, defined as recurrent attacks of fever

and at least 1 mutation detected in the MVK gene, were eligible for this study. All registered physicians of these patients received an additional questionnaire about clinical features, complications, course of disease, and response to therapy, and, where applicable, were asked to supply missing information. Patients were included when follow-up data were available up until January 2007 or until their death.

Quality of Life and Course of Life Assessment

For the assessment of quality of life and course of life we included only Dutch patients >16 years of age who had the ability to understand the standardized questionnaires in the Dutch language. The patients were approached by their treating physician, and after giving informed consent, received a letter with an explanation of the study and a questionnaire booklet. After 1 month a reminder letter and a new booklet were sent to those who did not respond. The questionnaire included 3 items:

The *Course of Life questionnaire*, a Dutch questionnaire, was used to assess the achievement of developmental milestones retrospectively in persons aged 16–30 years. This questionnaire was developed to investigate the course of life in persons who have grown up with a chronic or life-threatening disease compared to peers without a history of disease[17]. The validity of the course of life scales and the test-retest reliability are good[17]. For the current study we used 2 scales: development of autonomy and social development. In addition, the questionnaire measures sociodemographic outcomes in young adulthood, such as living situation, education, and employment. Data derived from a group of 508 Dutch controls were available for comparison[32].

The *RAND-36 Health Survey* was used to assess the quality of life and is almost identical to the MOS SF-36. The RAND-36 is the most commonly used health status measurement for assessing quality of life in the world. It measures 8 different health domains: physical functioning, role limitations due to physical health, social functioning, role limitations due to emotional problems, bodily pain, vitality, general health perception, and mental health. The validity and reliability of the RAND scales are satisfactory[40]. Norm data were available from a sample of 1036 persons[41].

Since the RAND-36 does not measure cognitive functioning satisfactorily, we added the cognitive function scale of the *TNOAZL Adult Quality of Life (TAAQoL)* questionnaire to the study. The TAAQoL is a validated, generic health-related quality of life questionnaire developed by researchers from TNO and the Leiden University Medical Center. The cognition scale consists of 4 items; a higher score indicates better cognitive functioning[15]. We compared the TAAQoL cognition score of the HIDS patients with the Dutch norms provided by Fekkes and colleagues[15].

The local ethical committee approved the study design.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) Windows version 14.02 was used for all analyses. We used the chi-square test to evaluate categorical data, and the Student t-test to compare the mean between groups. We

performed nonparametric Mann-Whitney U tests to test group differences in the number of attacks per year and the Friedman test to test for change of number of attacks during life. To adjust for multiple testing, a significance level of $p < 0.01$ was used for all tests of quality of life.

RESULTS

Demographic Features

Of the 126 patients with mutation-positive HIDS, 103 patients could be included in this study. Reasons for exclusion included no response from registered physician (n = 17) and loss to follow-up (n = 6). Excluded patients did not differ from included patients in current age, age of onset, or IgD concentrations (data not shown). The patients originated from 18 different countries on 3 different continents, although the majority of patients were European, or from European ancestry (Figure 1). The median current age of patients was 19.0 years (mean, 24.5 yr) with a range of 2–74 years (Table 1). The median age of onset of symptoms was 6 months, ranging from the first week of life to 10 years. Most patients had their first attack within the first year of life (78.1%); 6 patients had the first symptoms after the age of 4 years (Figure 2). The diagnosis of HIDS was made at a mean age of 15.7 years (median, 10.0 yr; range, <3 mo–52 yr). There was a mean delay to diagnosis of 13.9 years (median, 9.9 yr). In recent years the delay in time to diagnosis has not changed significantly. In patients with HIDS diagnosed after the year 2000 (n = 50), there was still a mean delay to diagnosis of 11.7 years (median, 8.4 yr). In 33 patients an alternative diagnosis was made before HIDS was diagnosed (Table 2).

Clinical Features

Attacks of fever were accompanied by an array of signs and symptoms (Figure 3). A typical attack of HIDS started with prodromal symptoms such as malaise and headache, followed by a rapid rise in temperature, often >40 °C. Cold chills accompanied fever in two-thirds of patients. Physical and emotional stress was recognized by many patients as a
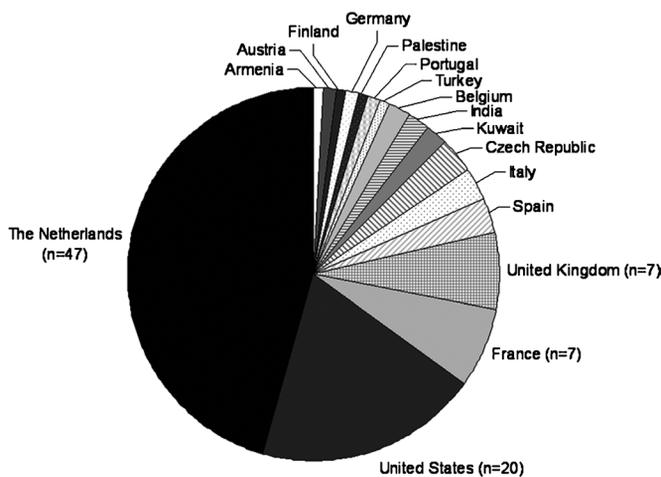
TABLE 1. Demographic Features

Feature		No. of Patients With Data Available
Current age, median in yr (range)	19.0 (2–74)	103
Sex (male:female)	52:51	103
Age at onset, median in yr (range)	0.5 (0–10)	96
Follow-up from onset, median in yr (range)	17.6 (2–74)	96

precipitating factor. Childhood vaccinations often induced the first attack; this was reported in 63% of patients.

Lymphadenopathy and Splenomegaly

Lymphadenopathy accompanied attacks in almost 90% of patients. The enlarged lymph nodes were generally painful on palpation and were located primarily in the cervical region. Axillary and inguinal localization occurred less frequently. Splenomegaly was found in 32.4% of patients, and all patients who had splenomegaly also had accompanying lymphadenopathy (Table 3).

Gastrointestinal Symptoms

Abdominal pain, vomiting, and/or diarrhea accompanied attacks in all but 5 patients. Abdominal pain could be severe and could resemble acute abdomen, tempting the attending physician to order exploratory surgery. At least 7 patients had surgery for suspected appendicitis. In 6 patients abdominal adhesions were found on exploratory surgery, suggesting repeated sterile peritonitis as the cause of abdominal pain.

Articular Symptoms

Arthralgia, a prominent feature of HIDS, was experienced by 83.5% of patients, making it the third most frequent symptom of HIDS after lymphadenopathy and abdominal pain. Fifty percent of the patients had arthritis, defined as swollen, tender joints. Information about the specific joint involved was available in 60 of 86 patients with arthritis and/or arthralgia (Figure 4). Arthralgia and arthritis were mainly restricted to large peripheral joints. In the
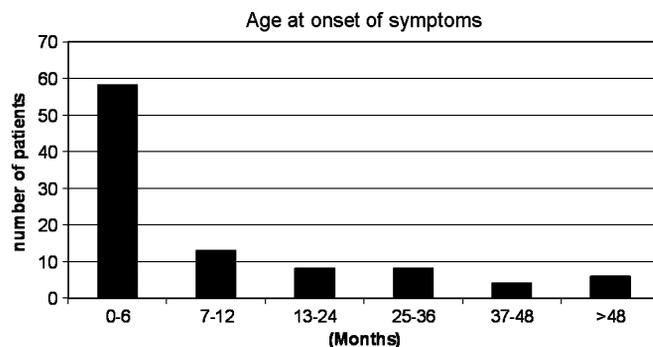

FIGURE 1. Country of origin of 103 patients with HIDS.

FIGURE 2. Distribution of age at onset of symptoms.

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TABLE 2. Incorrect Diagnoses Made Before HIDS Diagnosis

Diagnosis	No. of Patients
FMF	13
Adult-onset Still disease	6
JCA	5
Rheumatic fever	3
Chronic infection	3
Behçet disease	3

Abbreviation: JCA = juvenile chronic arthritis.

TABLE 3. Symptoms During Attacks

Symptom	% of Patients
Lymphadenopathy	87.4
Abdominal pain	85.4
Arthralgia	83.5
Diarrhea	71.6
Vomiting	70.9
Skin lesions	68.9
Headache	63.3
Cold chills	62.7
Arthritis	55.3
Aphthous ulcers	48.5
Splenomegaly	32.4
Hepatomegaly	21.6
Serositis	18.6

hands, both metacarpophalangeal and proximal interphalangeal joints may be affected.

Cutaneous and Mucocutaneous Manifestations

Skin manifestations accompanied attacks of fever in more than two-thirds of patients. Usually this was a maculopapular rash, but urticarial rash, purpura, and erythema nodosum have also been reported. Oral aphthous ulcers with or without accompanying genital ulcerations were reported in 48.5% of patients. That aphthous ulcers can be a very prominent symptom is illustrated by the fact that in 3 patients a diagnosis of Behçet disease was made before the diagnosis of HIDS.

Laboratory Results

All patients had a vigorous acute-phase response during attacks, with elevated ESR (median, 76 mm/h), leukocytosis (median, 15,000 per mm^3), and C-reactive protein (median, 163; range, 36–404 mg/L). Between attacks, some patients had continuous elevation of inflammation markers, although much lower than during attacks. An elevation of serum polyclonal IgD is considered a hallmark of the disease. The median IgD concentration of the highest IgD measured in the patients was 400 U/mL (range, <0.8–5300 IU/mL). However, an elevated IgD concentration was not universally present in HIDS patients: in 22% of patients, the highest concentration of IgD measured was below the upper limit of normal (<100 IU/mL).

Elevation of serum IgD is frequently accompanied by elevation of serum IgA. Data about serum IgA concentration was available for 86 patients. In 55 patients (64%), the IgA concentration was above the upper limit of normal of 2.6 g/L (median, 4.05 g/L).
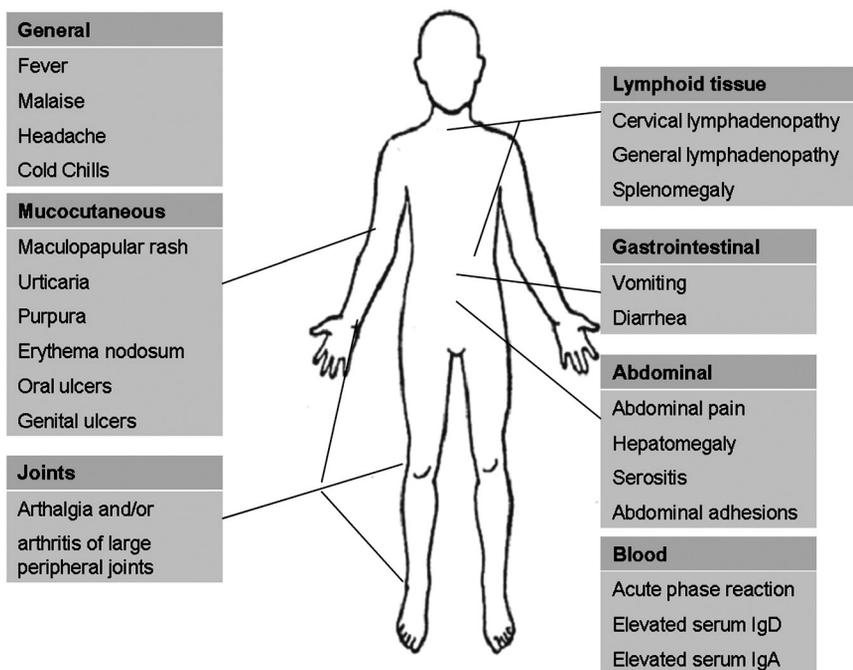

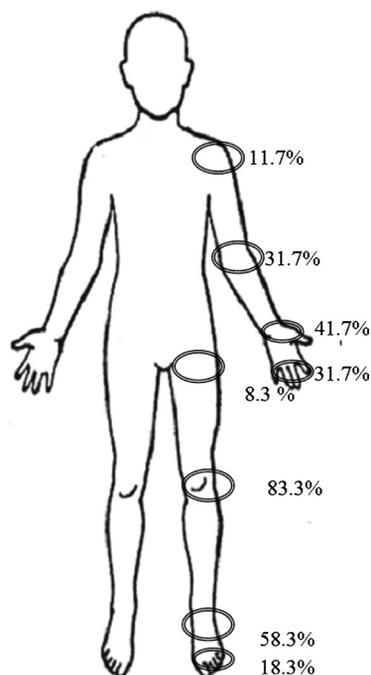**FIGURE 3.** Clinical features of HIDS.

FIGURE 4. The location of articular symptoms in HIDS, including arthralgia and arthritis. Note that more than 1 joint is often involved in a single patient.

Genetics

Table 4 shows the most prevalent mutations. The 4 most prevalent mutations accounted for 71.5% of mutations found. Only 4 patients did not have any of these 4 prevalent mutations. In 12 patients only 1 mutation was identified. Seventy-seven patients were compound heterozygote, while 14 patients were homozygote. We compared compound heterozygotes for V377I, I268T, H20P, P167L, and V377I homozygotes (n = 11) with patients who did not carry these mutations. There was no association between these genotypes and age of onset, symptoms during attacks, and number of attacks per year (data not shown).

Follow-Up: Course of Disease and Complications

Frequency of Attacks During Life

We asked physicians to indicate the number of attacks occurring in their patients. There was a significant decrease

TABLE 4. Allele Frequencies of MVK Mutations

Mutation	Allele Frequency (%)
V377I	50
I268T	14.7
H20P/N	4.4
P167L	2.4
H380R	1.5
R215Q	1.5
W188X	1.5
25 Other mutations and deletions	All <1
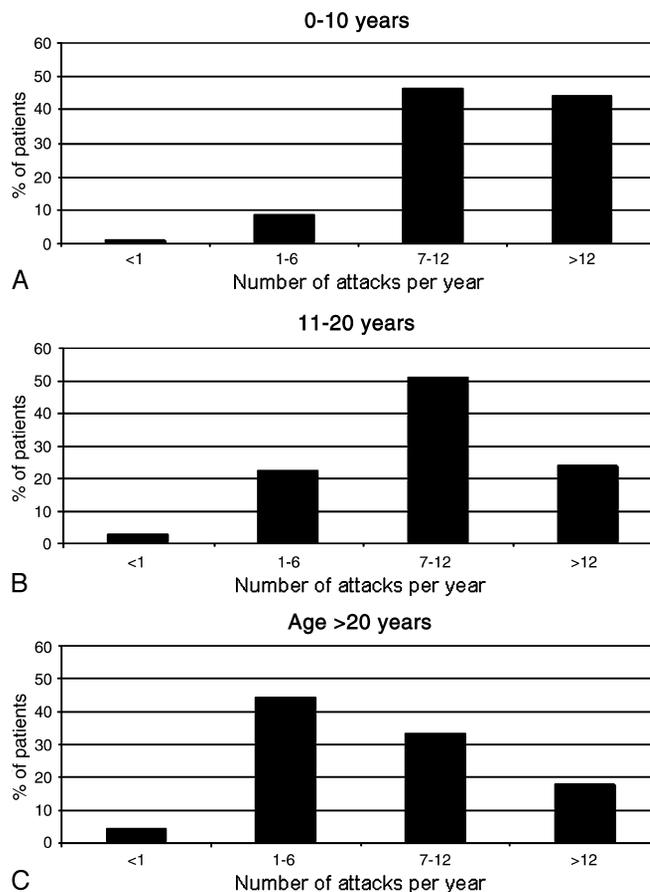
FIGURE 5. Number of attacks per year in the first decade of life (A), in the second decade of life (B), and after the age of 20 years (C), as retrospectively reported by patients' physicians.

in the frequency of attacks with increasing age (Figure 5), although no patients had a remission. In the first decade of life, 44.1% of patients had more than 12 attacks per year. This decreased to 23.9% in the second decade of life. After the age of 20 years, 17.8% of patients continued to

TABLE 5. Medications Tried and Response to Therapy in HIDS Patients*

	No Response (n)	Some Response (n)	Good Response (n)
Prednisone (n = 45)	17	17	11
Colchicine (n = 44)	37	7	0
Statin (n = 18)	12	4	2
Antibiotics (n = 13)	11	2	0
Etanercept (n = 13)	4	5	4
Anakinra (n = 11)	4	3	4
Thalidomide (n = 8)	7	1	0
Cyclosporine (n = 7)	6	1	0

*Patients may have used multiple medications.

TABLE 6. Characteristics of Patients Included in the Quality of Life Assessment

Median age, yr (range)	34.6 (16.5–67.5)
Median age at onset, mo	6
Mean disease duration, yr (range)	31.9 (16.3–65.1)
Male:female (n:n)	15:11
No. of attacks last year (n)	
<1	1
1–6	16
7–12	6
>12	3

have attacks more than 12 times per year, while 50% of patients still had more than 6 attacks per year (p = 0.001). Thirty-three of 45 patients above the age of 20 years had fewer attacks after the age of 20 years than in the first decade of life.

Amyloidosis

Type AA amyloidosis, a frequent complication in the other autoinflammatory diseases, was reported in 3 patients (2.9%) who have been described elsewhere[27]. All 3 patients had recurrent fevers for more than 20 years before the manifestation of amyloidosis. No additional cases of amyloidosis in HIDS were discovered in the current follow-up study.

Abdominal Adhesions

Repeated peritonitis, resulting in abdominal adhesions found during laparotomy, was reported in 10 patients.

Joint Contractures

Joint contractures as a result of arthritis was reported in 2 siblings aged 13 and 14 years, and in 2 brothers aged 17 and 27 years. None of the other patients manifested any signs of erosive arthritis.

Mortality

Three patients in the cohort died during the follow-up. The causes of death did not seem to be associated with HIDS symptoms or complications. The causes of death were suicide (patient aged 50 yr), cerebral hemorrhage (aged 61 yr), and pneumococcal sepsis (aged 31 yr).

Therapeutic Interventions

A wide variety of immunomodulatory drugs was tried to treat and prevent attacks in this cohort of patients (Table 5). Apart from the drugs listed in the table, the following medications have been tried with limited, if any, success: methotrexate, azathioprine, salazopyrine, tacrolimus, dapsone, intravenous immunoglobulins, montelukast, cimetidine, and ranitidine. When prednisone was given in high dosage at the onset of an attack, a considerable number of patients experienced a reduction in severity and duration of attacks (24.4% good response, 37.8% some response). Colchicine was ineffective in preventing or treating attacks in HIDS, in contrast to FMF. In 80% of patients in whom it was tried (n = 20) the biological agents anakinra and etanercept had at least some response. When anakinra is ineffective, patients may respond to etanercept, and vice versa.

Quality of Life and Course of Life

Thirty-eight patients were eligible for this study. Twenty-eight patients returned the quality of life questionnaire (73.7%). Patient characteristics are listed in Table 6. There was no significant difference between the study population and other patients from the cohort >16 years of age concerning prevalence of symptoms, age of onset, and number of attacks.

Health-Related Quality of Life

The RAND-36 dimensions social functioning, physical role functioning, general health perception, and vitality were significantly lower (p < 0.01) in patients than in the general
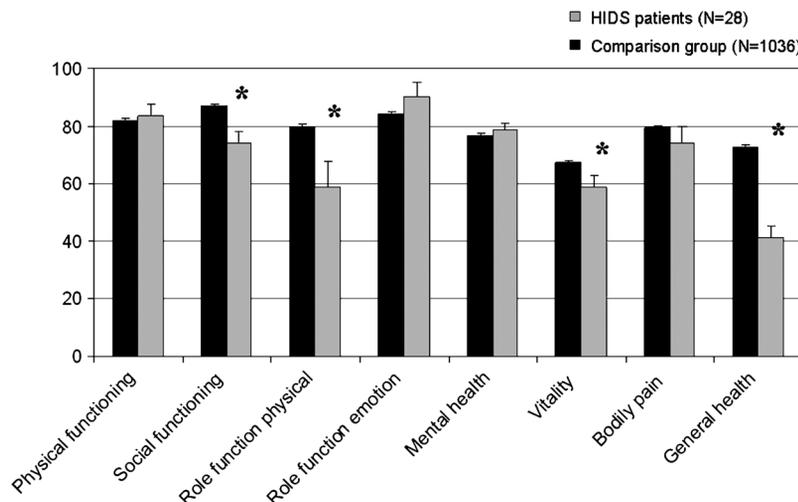

FIGURE 6. Comparison of health-related quality of life (RAND-36) in HIDS patients and in Dutch control group. Error bars represent SEM. *p < 0.01.

TABLE 7. Mean Scores and SD Between Patients With HIDS and Comparison Group on 2 Scales of the Course of Life Questionnaire

	HIDS (n = 14)	Comparison Group (n = 501)	p Value
Social development			
Mean	19.17	20.96	p = .01
SD	3.07	2.48	
Autonomy development			
Mean	8.31	9.87	p < 0.01
SD	1.18	1.48	

population (Figure 6). Patients who experienced more than 6 attacks in the past year scored significantly lower on the scales for pain (53.1 ± 11.6 vs. 87.3 ± 6.5; p < 0.01), physical role functioning (18.8 ± 12.3 vs. 80.8 ± 10.3; p = 0.01), and general health perception (27.5 ± 5.1 vs. 47.8 ± 5.0; p = 0.01) than patients with 6 or fewer attacks in the past year. There was no significant difference on the TAAQoL cognition scale between HIDS patients and the comparison group (data not shown).

Course of Life

Autonomy development and social development during childhood were significantly lower in patients with HIDS compared to controls (Table 7). In addition, 45.8% of patients indicated that their disease delayed their education, and in 17% this made high school graduation unachievable. During primary education, 44% had to repeat a year, while 41% of patients repeated a year during high school. Furthermore, 34.8% of patients reported that their disease contributed to discharge from their jobs. Currently, 26.6% of the patients were unemployed, a much higher percentage than in the general Dutch population (4.0%)[7].

DISCUSSION

The current study is, to our knowledge, the largest series of HIDS patients reported so far and the first to investigate the progression of disease and the effects of HIDS on quality of life. Although patients were entered into the database over a period of 14 years and patients originated from 18 different countries, we were able to obtain follow-up data from 81.7% of patients.

One purpose of the present study was to collect new data on clinical features of HIDS. The frequency of symptoms found in this study differs to some extent from the frequency found in our 1994 report of 50 patients in whom HIDS had been diagnosed based on purely clinical grounds—that is, recurrent fever episodes and persistent elevation of serum IgD[11]. In the current study we found more abdominal pain (85.4% vs. 72%), vomiting (70.9% vs. 56%), and headache (63.3% vs. 52%), while skin lesions (68.9% vs. 82%) and splenomegaly (32.4% vs. 48%) were reported less often. Furthermore, an onset of disease after childhood was not found in the current study. An explanation for this difference is that of the 50 patients in our initial

1994 study, only 31 patients later proved to have mutations in the MVK gene (22 of whom were also included in the present study). Two patients were later diagnosed as having TRAPS, 5 patients had a normal MVK gene upon testing, while in the remaining 12 patients, the clinical diagnosis of HIDS could not be confirmed at the molecular level because of a lack of biological material.

Our data indicate that HIDS is a difficult diagnosis to make. We found a median delay to diagnosis of 9.9 years after onset of symptoms. Although genetic testing has been available since the end of the last millennium, there continued to be a long delay to diagnosis in patients who were diagnosed after the year 2000. Furthermore, in many patients an alternative diagnosis was offered before the correct diagnosis of HIDS.

Aphthous ulcers can be a prominent feature in HIDS patients. These can be restricted to the oral cavity but can also include genital ulcers. Recently, in a genetic analysis of 96 patients who had a clinical diagnosis of Behçet disease, mutations in the MVK gene were found in 2 patients. Both patients had clinical characteristics of HIDS including recurrent fever attacks and arthralgia[21]. In our cohort, a diagnosis of Behçet disease was made in 3 patients who ultimately proved to have HIDS. Twelve patients had previously been diagnosed with FMF. HIDS can be distinguished from FMF on several grounds. First, FMF is rare in patients from other than Mediterranean or Jewish ancestry[35]. Furthermore, lymphadenopathy and aphthous ulcers, both important features of HIDS, do not accompany attacks in FMF[36]. In addition, HIDS does not respond to treatment with colchicine. Although raised IgD concentrations have been described in FMF patients, that is infrequent, and IgD concentrations rarely exceed 200 IU/L[23].

Elevation of IgD may provide a clue to the diagnosis, but it is not diagnostic. Although the majority of patients have an elevated IgD concentration, in 22% of patients IgD values were normal. This is in line with other observations[1,9,19,29]. Furthermore, an elevation in serum IgD has been described in other autoinflammatory diseases[10,26].

TABLE 8. Clinical Guideline for When to Consider Testing for HIDS

Consider testing for HIDS if patient has

Recurrent fever episodes lasting 3–7 days persisting more than 6 months

AND 1 or more of the following:

1. Sibling with genetically confirmed HIDS
2. Elevated serum IgD (>100 IU/L)
3. First attack after childhood vaccination
4. Three or more of the following symptoms during attacks:
   - Cervical lymphadenopathy
   - Abdominal pain
   - Vomiting or diarrhea
   - Arthralgia or arthritis of large peripheral joints
   - Aphthous ulcers
   - Skin lesions

In addition, we have previously found that IgD levels do not correlate with inflammatory symptoms[30].

This suggests that IgD should not be a requirement for diagnosis, but can assist in making the diagnosis. Based on our experience, we suggest a set of clinical characteristics that may serve as a guideline in the rational ordering of genetic tests (Table 8). A diagnosis of HIDS should be entertained in patients with the following:

Recurrent episodes of fever lasting 3–7 days persisting more than 6 months AND
Elevated serum IgD (>100 IU/L) *or*
Sibling with confirmed HIDS *or*
First recorded attack after childhood vaccination *or*
At least 3 of the following symptoms during attacks: cervical lymphadenopathy, abdominal pain, vomiting or diarrhea, arthralgia or arthritis of large peripheral joints, aphthous ulcers, and skin lesions.

Applying these criteria to our cohort, all patients would be identified. However, this suggested guideline has not been tested yet for its discriminative power in unselected patients presenting with recurrent fever.

In the current study we did not find a relationship between the 4 most prevalent mutations and the severity of the phenotype. A possible bias could be that we include in the database only patients who have a HIDS phenotype, therefore excluding patients with the most severe phenotype associated with MVK mutations, that is, MVA. MVA is, in addition to fever attacks, characterized by psychomotor retardation, progressive cerebral ataxia, dysmorphic features, and progressive visual impairment[18]. Mandey et al[25] could differentiate MVA and HIDS patients based on their genotype: MVA patients never possess a V377I allele. However, in a patient group restricted to HIDS, Cuisset et al[8] also failed to find a genotype-phenotype relationship.

We observed a gradual decrease in the frequency of attacks during a patient's life, although after the age of 20 years, half the patients still had attacks at least every other month.

Long-term complications in our patient cohort consisted of renal amyloidosis (n = 3), joint contractures (n = 4), and abdominal adhesions (n = 10). The occurrence of adhesions in the absence of prior surgery indicates that the abdominal pain in HIDS attacks may be due to sterile peritonitis, analogous to that in other autoinflammatory syndromes. The incidence of amyloidosis was remarkably low compared to other periodic fever syndromes[33,35].

Recent developments have improved the treatment of HIDS. The data in this cohort indicate that it may be a reasonable strategy first to try using prednisone in a patient with HIDS, starting at the first signs of attack. When this is ineffective or insufficient, treatment with a biological agent should be considered. A dose of 100 mg anakinra or 25 mg etanercept subcutaneously at the first signs of an attack has recently shown beneficial effects in a number of case reports[2,3,6,34], although randomized trials are lacking. If either anakinra or etanercept is not effective, a switch to the other can be considered, since some patients have good response to anakinra but not etanercept, and vice versa. In mildly affected patients, simvastatin can safely be tried to reduce the number of days of illness without side effects[31], although the present study highlights its limited efficacy. There does not appear to be a role in the treatment of HIDS for other immunosuppressive and immunomodulatory agents, or for continuous antibiotics.

In the current study we show that HIDS adversely influences several aspects of quality of life. Although patients were capable of performing physical activities as measured by a physical functioning scale, they did experience limitations in daily activities due to their disease. Furthermore, HIDS has an unfavorable effect on the social functioning of patients. Buskila et al[5] found similar results in a study on the quality of life in FMF patients. Although Buskila and colleagues used a different instrument to measure quality of life, they found a negative effect on social functioning and independence.

It is known that parents of chronically ill children tend to overprotect their sick children[28]. Chronic diseases in children often increase their dependence on caregivers and decrease the participation in peer and school activities[33]. This may explain the impairment in social development and in the development of autonomy we found. But since this questionnaire was developed for and validated in adolescents and young adults (aged 16–30 yr), we could include only 14 patients in the analyses of these items. Although there is a significant difference between patients and controls, we should be cautious about drawing firm conclusions.

No less than 42.9% of patients indicated that HIDS prolonged their school career, and 26.6% of patients were unemployed. It cannot be inferred from these data whether the lack of educational and occupational achievement might result in part from neurocognitive impairment due to the metabolic defect itself. In any case, the febrile attacks do interfere with a normal school career, and if this can be prevented by effective antiinflammatory therapy, educational and social outcomes may improve.

The results of the present study of quality of life are relevant to clinical practice. Knowledge about possible gaps in the development in the course of life and about dimensions of child development that are affected by HIDS enables physicians to focus attention on these subjects, and to offer counseling where necessary. For example, pediatricians could help parents to stimulate and encourage the independence of their child.

In conclusion, HIDS is a severe disease that starts early in life with lifelong recurrent attacks of fever accompanied by a variety of symptoms, including lymphadenopathy, abdominal pain, arthralgia, vomiting and diarrhea, skin lesions, and aphthous ulcers. In the current series of 103 patients, we found a considerable delay to diagnosis (median, 9.9 yr). There is a gradual decrease in the number of attacks with increasing age, although half the patients over 20 years of age continued to have more than 6 attacks per year. Prednisone, anakinra, and etanercept can be effective in some patients in reducing the severity of attacks. HIDS adversely affects several aspects of the quality of life and interferes with educational achievements and employment status. Infrequent but severe complications of HIDS include amyloidosis (2.9%), joint contractures (3.9%), and abdominal adhesions (9.7%).

APPENDIX

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