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ORIGINAL ARTICLE

Incidence and clinical features of hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) and spectrum of mevalonate kinase (MVK) mutations in German children

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Abstract Autoinflammatory diseases (AIDs) are characterized by recurrent, self-limiting systemic inflammation. Disorders include hereditary recurrent fever (HRF) syndromes such as hyperimmunoglobulinemia D and periodic fever syndrome (HIDS). To determine the incidence of HIDS and report clinical and genetic characteristics together with the underlying *MVK* genotypes in German children, a prospective active surveillance was conducted in Germany during a period of 3 years. Monthly inquiries were sent to 370 children's hospitals by the German Paediatric Surveillance Unit (Clinic-ESPED, n1) and to two laboratories (Laboratory-ESPED, n2) performing genetic analyses. Inclusion criteria were a *MVK* mutation–positive patient ≤16 years of age with more than three self-limiting episodes of fever >38.5°C associated with increased inflammation markers. Clinical, epidemiological, and genetic data were assessed via questionnaires. Eight out of 16 patients were identified in Clinic-ESPED (n1) and 15 of 16 in Laboratory-ESPED (n2). Clinical and laboratory surveys overlapped in 7 of 16 cases. Incidence of HIDS was estimated to be 0.39 (95% CI: 0.22, 0.64) per 10^6 person-years. HIDS symptoms generally started in infancy with recurrent fever episodes lasting 3–12 (median, 4.5) days and recurring every 1–12 weeks. Fever was accompanied by abdominal pain, vomiting, diarrhea, cervical lymphadenopathy, and sometimes by headache, skin and joint symptoms. The patients carried 11 different *MVK* mutations mostly in compound heterozygosity (75%, 12 out of 16). The most frequent mutation was p.Val377Ile (81%, 13 out of 16). In Germany, the incidence of HIDS is very low with 0.39 per 10^6 person-years.

Keywords HIDS · MVK gene · HRF · Autoinflammatory disease · ESPED

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Abbreviations

AID	Autoinflammatory disease
MVK	Mevalonate kinase
HIDS	Hyperimmunoglobulinemia D and periodic fever syndrome
MKD	MVK deficiency
HRF	Hereditary recurrent fever syndromes
ESPED	German Paediatric Surveillance Unit for rare paediatric diseases

Introduction

Hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) is a rare, autosomal recessively inherited

autoinflammatory disease caused by loss-of-function mutations in the mevalonate kinase (*MVK*) gene encoding mevalonate kinase [1–3]. Mevalonic aciduria represents the most severe phenotype of the wide clinical spectrum of mevalonate kinase deficiency [4]. The classical form of HIDS due to partial MVK deficiency is present in about 75% of known cases. MVK is an enzyme of the isoprenoid biosynthesis pathway that produces numerous biomolecules involved in a variety of cellular processes. The role of IgD, a potent inducer of cytokines in vitro, in the pathogenesis of HIDS remains, however, enigmatic [5]. Diagnosis of MKD relies first on biochemical tests revealing the enzymatic defect (the presence of mevalonate in urine (during fever episodes in HIDS) and/or decrease in the mevalonate kinase activity during the asymptomatic interval) and second on confirmation by DNA sequence analysis [6, 7].

The epidemiology and clinical manifestation of HIDS as well as the spectrum of *MVK* mutations in Germany are unknown. Therefore, we estimated the incidence of this disorder and analyzed the clinical and mutational spectrum in a paediatric population-based sample, using two independent methods for case ascertainment.

Methods

Study design

A prospective national active surveillance on hereditary recurrent fever (HRF) syndromes was conducted in Germany from July 2003 until June 2006 by the German Paediatric Surveillance Unit for rare paediatric diseases (ESPED) [8, 9]. Monthly inquiries were sent to 370 children's hospitals (Clinic-ESPED, n1) and to two laboratories specialized in genetics of HRF and performing genetic analyses of the *MVK* gene (Laboratory-ESPED, n2).

Case definition

The criteria for case definition included the following: age $\leq$16 years, confirmed *MVK* mutation, and more than three self-limiting episodes of fever >38.5°C of unknown origin associated with increased inflammation markers.

Newly diagnosed patients with a mutation in the *MVK* gene were added to the database, and epidemiological, clinical, and genetic information was collected using questionnaires for hospitals and laboratories. The return rates were 97% for the monthly report cards of Clinic-ESPED and above 90 and 98%, respectively, for the questionnaires of Clinic-ESPED and Laboratory-ESPED.

For each patient, the following data were documented in the Clinic-ESPED (n1): unique identification number, number and town of reporting clinic, core data (gender, date of birth (month/year), time of diagnosis (month/year)), history (consanguinity, ethnic origin and affected relatives), symptoms (description of fever episodes, skin, joint, abdominal, neurological, and bone involvement, lymphadenopathy, serositis, amyloidosis, trigger, rare observations), inflammation markers, genetic analysis and medication (NSAIDs, corticosteroids, colchicine, etanercept, other medication like simvastatine and anakinra); and in the Laboratory-ESPED (n2): core data (gender, date of birth (month/year), time of diagnosis (month/year)), reporting institution (children's hospitals or paediatric private practices), patient or relative, genetic analysis, and laboratory methods (in 10 patients, exons 9 and 11 were sequenced; in 11 patients, exons 2,3, and 5–11 were analyzed; in 11 patients, exons 2–11 were sequenced; and in 11 patients, a sequence analysis of all exons was performed).

Incidence calculation

The number of cases reported (numerator) was calculated as the sum of cases reported from either source minus those reported in both data sources (n1 $\cap$ n2) to avoid double counting of the cases [n1 $\cup$ n2 = (n1 + n2) − (n1 $\cap$ n2)]. The identification of cases reported to both ESPED surveys was possible by using the core data of the patients. The denominator was the sum of children $\leq$16 years of age (y1 + y2 + y3) in 2004 (y1), 2005 (y2) and 2006 (y3) and correspond to person-years. A 95% confidence interval (CI) for the total number of cases was estimated assuming a Poisson distribution. This strategy gives a conservative estimate of the total number of cases without making any assumptions regarding possible dependencies between the sources. For calculation of the incidence per person-years in the complete population of German children $\leq$16 years of age, data of the Federal Office of Statistics were used (http://www.destatis.de).

Statistical analysis and data protection

Frequency measurements were carried out by descriptive analysis of each variable. Because of their apparently non-Gaussian distribution, continuous data are presented as medians and ranges. Discrete variables are described with proportional values.

Personal data were analyzed anonymously. With the information kept in the data bank, it was impossible to retrieve the identity of individuals. Data were also protected against unauthorized access. The study has been approved by the ethics committee at the University of Düsseldorf. Parents and patients were instructed by an information letter.

Results

Incidence of newly diagnosed HIDS

A total of 156 cases of HRF and among these 8 (5%) cases of mutation-positive HIDS were reported in Clinic-ESPED (n1) between 2003 and 2006. Altogether, 16 cases in 10 families fulfilled the inclusion criteria and were recorded in at least one of the two surveillance systems (n1 or n2). Out of these, 7 (44%) were identified in both sources (n1 ∩ n2). One case was documented only in Clinic-ESPED (n1), and eight cases were reported only in Laboratory-ESPED (n2).

We used the number of cases fulfilling the inclusion criteria for each of the two sources for 40,720,351 person-years of children ≤16 years under observation during the years 2003–2006 (13,863,624 + 13,572,071 + 13,284,656 in the first, second and third years of observation, respectively; cumulative person-years based on the annual number of children exposed; data of the Federal Office of Statistics), to determine the incidence of HIDS in Germany yielding an incidence of 0.39 (95% CI: 0.22, 0.64) per 10^6 person-years. The prevalence of HIDS in children less than 16 years of age during the 3 years of observation may be calculated by multiplying the incidence per person-years with 16, resulting in an estimate of 6.2 (95% CI: 3.5, 10.2) per 10^6 person-years in this age group.

Clinical presentation of HIDS patients

All cases fulfilled the inclusion criteria: age ≤16 years, confirmed *MVK* mutation and more than three self-limiting episodes of fever >38.5°C of unknown origin associated with increased inflammation markers. More detailed clinical information was available for 8 out of 16 cases. These eight data sets of HIDS children (four girls and four boys) recorded in the Clinic-ESPED survey showed an age of 1–2 years for onset of attacks (Table 1). HIDS started in infancy with recurrent fever episodes lasting 3–12 (median, 4.5) days and recurring every 1–12 weeks. Fever was typically accompanied by abdominal pain, vomiting, diarrhea, cervical lymphadenopathy and sometimes by headache as well as skin and joint symptoms. The correct diagnosis was delayed by 1–13 (median, 6.5) years after symptom onset. A brother (case 3) with a heterozygous V377I mutation and a father (cases 6 and 7) with a heterozygous G25G substitution were identified as asymptomatic relatives. Affected relatives were present in two families with symptoms during childhood: a father (case 2) with only a clinically defined diagnosis and a mother (cases 6 and 7) with a compound heterozygous V377I/I268T genotype. Therapy was supportive. Three patients preferred on-demand treatment with corticosteroids and two children a permanent low-dose corticosteroid therapy. Three children were treated continuously with simvastatine and two patients with azathioprine. One patient did not receive drug treatment.

Genetics

Altogether, autosomal recessively inherited *MVK* mutations were identified by genetic analyses in 32 individuals (Table 2). The analysis included symptomatic and asymptomatic patients as well as relatives. Laboratory-ESPED (n2) detected 31 *MVK* mutation carriers consisting of three symptomatic and eight asymptomatic children identified in private practices and 12 symptomatic and eight asymptomatic carriers identified in children's hospitals. One out of 32 *MVK* mutations was only identified by Clinic-ESPED (n1). Seventeen different *MVK* mutations were detected in both surveys (Fig. 1). Ten mutations were novel. These rare mutations were classified as disease associated if they occurred (1) in patients with clinical disease, (2) in heterozygosity with frequent mutations that had been previously described with disease association, (3) encoded structural *MVK* variants or (4) resulted in complete loss-of-function of the enzyme. Mutations were detected in exons 1, 2, 3, 5, 8, 9 and 11. Most of them were missense mutations.

Sixteen children fulfilled the inclusion criteria and were diagnosed as classical symptomatic HIDS by children's hospitals and/or laboratories. Interestingly, 11 different *MVK* mutations were identified in these 16 patients pointing to a high degree of genetic heterogeneity (Fig. 1). The large majority of patients (12 out of 16) were compound heterozygous for two mutations (75%). The most common *MVK* mutation (81%, 13 out of 16) was p.Val377Ile.

Discussion

Sixteen cases of HIDS were identified by means of a 3-year active surveillance using data sources in Germany, accounting for an incidence in children of 0.39 (95% CI: 0.22, 0.64) per 10^6 person-years. The most common *MVK* mutation was p.Val377Ile in compound heterozygosity.

Underreporting is a potential critical issue pertaining to our data as not all HIDS patients might be hospitalized or seen by a paediatric specialist. Twelve out of 16 symptomatic children were reported from hospitals and three cases by private practices in Laboratory-ESPED (n2) and one case in Clinic-ESPED (n1) by hospital only. Patients from private practices have not been included in the Clinic-ESPED (n1). However, it may be assumed that the more severe cases had been hospitalized to exclude potentially

Table 1 Clinic-ESPED: clinical and genetic characteristics of eight newly diagnosed HIDS patients reported between 2003 and 2006

						Abdomen			Joint		Skin and muscle			Head and neck		General				
Case	Age at onset of attacks (years)	Age at diagnosis (years)	Origin	Duration of fever episode (days)	Mutation in the *MVK*-gene	Abdominal pain	Vomiting	Diarrhoea	Backache	Arthralgia	Myalgia	Aphthosis	Exanthema	Conjunctivitis	Headache	Lymphadenopathy	Trigger factors	Rare observations	IgD IU/ml (normal < 100 IU/ml)	Drugs
1	1	14	German	4	p.Val377Ile/ p.Ala28Thr	x	x	x	x				x		x	x	x		1210	cor
2	2	10	German	12	p.Val377Ile/ p.Met1Leu	x	x	x		x	x		x	x	x	x			1400	no
3	1	7	German	5	p.Val377Ile/ p.Val377Ile	x				x	x		x		x			Foeter ex ore, pharyngitis	480	simv, cor
4	1	6	German	3	p.Val377Ile/ p.Ile268Thr	x		x		x					x	x		Pharyngitis, infections of respiratory tract	340	cor, aza
5	1	8	German	7	p.Val377Ile/ p.Ile268Thr	x	x	x							x	x		Infections of respiratory tract, encephalitis	144	cor, aza
6	1	2	German/ Bosnian	4	p.Gly25Gly/ p.Arg277His	x	x	x				x	x			x			<100	simv
7	1	2	German/ Bosnian	4	p.Gly25Gly/ p.Arg277His	x	x	x				x	x			x			<100	simv
8	1	8	German	5	p.Val377Ile/ p.Ser378Pro	x	x			x					x	x		p.Arg121Gln (*TNFRSF1A* gene)	129	cor

Drugs: *cor,* corticosteroid; *simv,* simvastatine; *aza,* azathioprine; *no,* none; cases 4 and 5 are brothers [10]; cases 6 and 7 are monozygotic twins [11]; case 8 has a *TNFRSF1A* and two *MVK* mutations [12]

dangerous differential diagnoses such as autoimmune or oncologic diseases. Nevertheless, among the hospitalized cases, underreporting was seen because Clinic-ESPED (n1) failed to identify four hospitalized cases. Failure to diagnose might also be an issue accounting for underestimation of the true incidence. The delay in correct diagnosis is due to the fact that symptoms manifested by patients with HIDS are unspecific and frequently found in very common illnesses, which are usually excluded before rarer diagnoses are considered. The periodic pattern of symptom recurrence is often the clue that finally leads to the correct diagnosis.

More than 60% of the HIDS patients worldwide are of Dutch or French ancestry, although HIDS cases have been reported from around the world. The Nijmegen patient registry was initiated in 1992 and holds data on more than 200 patients (http://www.hids.net) [13, 14]. Population genetic studies in the Netherlands suggested a disease incidence between 1 in 5,196 and 1 in 53,656. The incidence estimation for clinically manifest cases in Germany based on our data, in contrast, is 1 in 2,564,102 which is about 50-fold lower than even the lowest estimated incidence rate in the Dutch population. This dramatic discrepancy may reflect differences in the genetic makeup of the Dutch and German population. It is probably also the result of a reduced penetrance of some mutations in the *MVK* gene, which may lead to an underascertainment of HIDS cases [5, 15, 16].

Van der Hilst et al. described the long-term follow up of 103 HIDS patients (Table 3). The majority of patients had their first attack within the first year of life (78%). There was a median delay to diagnosis of 9.9 years. In 33 patients, an alternative diagnosis was made before HIDS was diagnosed (e.g. FMF, juvenile idiopathic arthritis, rheumatic fever, chronic infection and Behçet's disease). In general, HIDS patients have a normal life span and rarely suffer any serious complications of the disease, rare exceptions being the occurrence of amyloidosis (2.9%), abdominal adhesions due to sterile peritonitis (9.7%) and joint contractures (3.9%) [17].

There is a great individual and interfamilial variability of the clinical HIDS features. A common definition of

Table 2 Spectrum of *MVK* mutations in all symptomatic or asymptomatic children in Germany

Mutations in the *MVK* gene	Compound heterozygous	Homozygous	Heterozygous	Mutations in INFEVERS database*
p.Val377Ile/p.Ala28Thr	**1**			Yes/no
p.Ile268Thr/p.Thr237Ser	**1**			Yes/yes
p.Val377Ile/p.Met1Leu	**1**			Yes/no
p.Val377Ile/p.Ser378Pro	**1**			Yes/yes
p.Val377Ile/p.Gly140ArgfsX47 (c.417_418insC)	**1** + 1			Yes/no
p.Val377Ile/p.Lys355AsnfsX4 (c.1071delG)	**1**			Yes/no
p.Val377Ile/p.Leu264Phe	**2** + 1			Yes/yes
p.Val377Ile			**2** + 3	Yes
p.Val377Ile		**2**		Yes
p.Val377Ile/p.Ile268Thr	**2**			Yes/yes
p.Gly25Gly/p.Arg277His	**2**			Yes/yes
p.Ser378Pro			1	Yes
p.Asp269His			1	No
g.4967C > A (NG_007702.1)			2	No
p.Val377Ile/p.Ala10Val	1			Yes/no
p.Val377Ile/p.Ile286Thr	1			Yes/no
p.Ile286Thr			1	No
c.1245insG			1	No
p.Ser362Ile			2	No
p.Ala28Thr			1	No
Total number of symptomatic cases in n1 and n2 (bold)	**12**	**2**	**2**	**16**
Total number of asymptomatic and symptomatic cases in n1 and n2	16	2	14	32

Significance of bold represents symptomatic patients in Clinic- and Laboratory-ESPED

* Data freely available at http://fmf.igh.cnrs.fr/ISSAID/infevers/

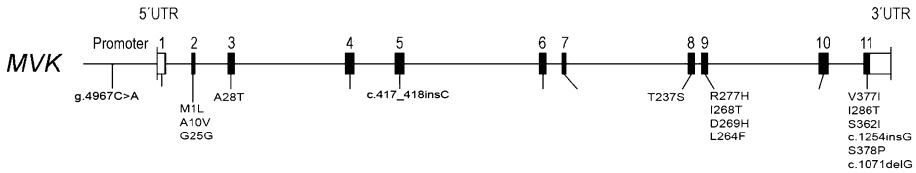

Fig. 1 *MVK* sequence variants and their location with respect to the exons

disease activity therefore would be useful in the management of this disorder [20]. Van der Hilst et al. published clinical guidelines as to when genetic testing for HIDS should be considered: recurrent fever episodes of 3–7-day duration for >6 months with an age of onset <5 years 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, vomiting or diarrhea, abdominal pain, arthralgia, arthritis of large peripheral joints, aphthous ulcers and/or skin lesions [21].

Steichen et al. presented a clinical criterion to exclude HIDS without the need of genetic testing in 149 patients. If genetic testing had been performed only in patients with a positive composite criterion [onset age <5 years or joint pain during attacks and length of attacks <14 d, (sensitivity of 100%, specificity of 28%)], no mutation-positive patient would have been missed, and 18 tests (19%) would have been avoided [22].

Gattorno et al. developed a diagnostic score and a flow chart for the molecular analysis of HRF. Additional information is available on the World Wide Web at http://www.printo.it/periodicfever [18]. Moreover, a preliminary activity score for each AID was created, with the score for HIDS (range 0–16) considering abdominal pain, diarrhea, nausea/vomiting, fever, limb pain and painful lymph nodes [20].

Nevertheless, genetic analysis is certainly at present the most important tool for confirming the tentative diagnosis. Although the incriminating gene was discovered in 1999, the exact mechanism of inflammation in HIDS has not been

Table 3 Percentage of HIDS children with specific symptoms

Number of cases(*n*=)	Abdominal pain	Splenomegaly	Hepatomegaly	Vomiting	Diarrhoea	Artrhritis	Arthralgia	Myalgia	Aphthosis
Van der Hilst et al. [17] 103	85	32	22	71	71	50	84		49
Gattorno et al. [18] 18	100	50		72	72	17	72	50	39
D'Osualdo et al. [19] 15	100	47		80	80		80	60	
Lainka et al. 8	100			75	75		50	25	25

Number of cases (*n*=)	Pharyngitis	Exanthema	Conjunctivitis	Headache	Lymphadenopathy	Pain in cervical lymphnodes	Trigger factors	Serositis	IgD IU/ml
Van der Hilst et al. [17] 103		69		63	87			19	<100–5300
Gattorno et al. [18] 18	39 ex 78 ery	56	17	50	94	72		6	
D'Osualdo et al. [19] 15		47			100				<100–1910
Lainka et al. 8	25	63	13	75	88		13		<100–1400

Ex exsudative; *ery* erythematous, rare observations: Gattorno et al. [18]: periorbital edema 11%, thoracic pain 6%

elucidated [1, 2]. There is strong evidence that HIDS is not due to excessive IgD, because there are well-documented patients who have the HIDS phenotype and *MVK* mutations but persistently normal IgD levels, and even among patients with increased serum IgD, the levels do not predictably fluctuate with attacks [23].

MVK mutations are found throughout the gene and are mostly missense mutations [24]. The p.Val377Ile substitution is the most common mutation (52–90%) in compound heterozygous HIDS patients and results in modest decreases in enzymatic activity [25]. This mutation exhibits a founder effect in the Dutch population and likely explains the higher prevalence of HIDS in this population. Population-based studies indicate that 0.6% of Dutch people carry this particular alteration. Given the marked underrepresentation of homozygous p.Val377Ile patients in HIDS cohorts, it has been suggested that the homozygous state results in either a milder phenotype or none at all [5].

A major area of interest is the identification of factors affecting penetrance. Although genetic testing enables confirmation of the clinical diagnosis, there is still a large group of patients fitting the clinical phenotype in whom no mutations can be found; this is true for over 50% of probands with specific AID [26]. Unknown genes, allelic and loci heterogeneity, or modulator effects by different loci are suspected to explain the absence of mutations in those children with very suggestive clinical pictures [27]. Additionally, patients with a combination of mutations in two HPF genes (e.g. in the *MEFV* and *TNFRSF1A*-gene) have been reported, which can modify the phenotype [12, 28].

In children with a suspicion of a periodic fever syndrome, an accurate clinical history and a physical examination remain the first diagnostic tools [14]. Clinical vigilance in combination with a diagnostic strategy including close interaction between clinicians, laboratories, and geneticists is fundamental to diagnose patients with AID [11, 27]. A decision tree and scores can help in the diagnostic evaluation of children with periodic fever. It could optimize molecular analyses by suggesting the order in which the genes should be screened [29]. The therapy is still supportive and performed on an individual basis in affected patients, as therapeutic guidelines are lacking. Finally, many patients with periodic fever do not fall in one of the above-mentioned disease categories. It is to be expected that in the future, other periodic fever syndromes and associated genes will be discovered.

Research in the field of rare AIDs would be significantly improved if a sufficient number of patients were accessible. Electronic patient registries can help to provide the basis for this by collecting both retrospective and prospective data over a longer period of time and integrating centers on a national and even international scale [30].

Therefore, a German clinical and research consortium (AID-Net) was established in 2009, including an online registry for AID (accessible via http://www.aid-register.uk-essen.de), biomaterial banks (DNA/serum) and basic research projects that focus on molecular mechanisms of AID. The translational approach of AID-Net combines projects on epidemiology, clinical and immunological features as well as on molecular genetics [31].

Conclusions

Five percent of the patients with a newly diagnosed HRF are *MVK* mutation positive. The incidence of HIDS in Germany is very low, calculated as 0.39 per 10^6 person-years for the period 2003–2006. This corresponds to 1–10 newly diagnosed young patients per year. The disease-associated p.Val377Ile substitution is the most common mutation in compound heterozygous *MVK* genotypes. The rarity of HRFs and the limited diagnostic significance and prognostic value of associated mutations in children with fever of unknown origin currently do not appear to justify genetic screening in all children with fever. Clinical guidelines and scores for genetic testing are needed and should be validated to avoid uncritical use of costly mutational analyses and to improve disease management.

Key messages

The incidence of HIDS in Germany is very low and is calculated as 0.39 cases per 10^6 person-years.
The most common *MVK* mutation is p.Val377Ile in compound heterozygosity.

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Conflict of interest All authors declared no conflicts of interest.

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