A Clinical Criterion to Exclude the Hyperimmunoglobulin D Syndrome (Mild Mevalonate Kinase Deficiency) in Patients with Recurrent Fever

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ABSTRACT. Objective. The hyperimmunoglobulin D syndrome (HIDS) is an autosomal recessive autoinflammatory disease caused by mutations in the mevalonate kinase gene. Our objective was to define a clinical criterion able to exclude HIDS without the need of genetic testing.

Methods. A recursive partitioning algorithm was applied to derive the clinical criterion in 149 patients with genetic testing in a French laboratory, among whom 35 had HIDS. The criterion was validated in 93 patients with genetic testing in a Dutch laboratory, among whom 28 had HIDS.

Results. The most discriminatory composite clinical criterion satisfied by all patients with HIDS in the derivation group was [onset age < 5 years old OR (joint pain during attacks AND length of attacks < 14 days)]. It had a sensitivity of 100% (95% confidence interval 88% to 100%) and a specificity of 28% (95% CI 17% to 40%) in the validation group. If genetic testing had been limited to patients fulfilling this criterion, 18 tests (19%) would have been avoided in this highly selected validation sample, without missing a single patient with HIDS.

Conclusion. Even among patients already selected by expert physicians, this criterion could help prevent unnecessary genetic testing, which is resource- and time-consuming. (First Release June 15 2009; J Rheumatol 2009;36:1677–81; doi:10.3899/jrheum.081313)

Key Indexing Terms:
MEVALONATE KINASE DEFICIENCY
CLINICAL PREDICTION RULE
GENETIC SCREENING
SENSITIVITY AND SPECIFICITY
FEVER

Patients with recurrent febrile attacks without an apparent infection pose a diagnostic challenge to clinicians. A cause to be considered is the hyperimmunoglobulinemia D and periodic fever syndrome (HIDS). HIDS is a rare autosomal recessive disease that belongs to the group of autoinflammatory syndromes. Typical patients have an onset of disease in the first year of life with febrile attacks that last 3–7 days, recur every few weeks and are accompanied by cervical lymphadenopathy, joint pain, and gastrointestinal distress. However, beyond this typical presentation, there is a considerable variability in onset of disease and in clinical manifestations. Similarly, a marked elevation of polyclonal immunoglobulin D was first found in the serum of patients with HIDS, but this feature is not universally present and can also be found in some patients with other periodic fever syndromes.

In 1999, 2 groups separately discovered that HIDS is caused by a mutation in the mevalonate kinase gene (MVK), located on the long arm of chromosome 12 (12q24). This allowed genetic testing as a new diagnostic tool. Although genetic testing for HIDS is currently possible, its availability is usually limited to specialist referral centers. Further, it is a time-consuming and expensive test. Genetic testing for HIDS is considered in patients with recurrent fever of unknown origin. Our aim was to develop a criterion based on clinical features that can exclude HIDS in these patients without performing genetic tests.

MATERIALS AND METHODS
Derivation group. Patients were considered for inclusion in the derivation group if they were tested for MVK mutations in a single French reference laboratory from February 2002 to August 2007. Coding exons (2 to 11) of the MVK gene were entirely sequenced including exon/intron boundaries. When the clinical presentation was not suggestive of HIDS — according to the typical features highlighted above — genetic testing was performed only after ascertaining that the MVK enzyme activity was low. MVK enzyme activity was determined in peripheral blood lymphocytes using a
radiometric assay and residual activity between 1% and 30% of controls was considered indicative of HIDS. Patients with mevalonic aciduria or with a family member who had already tested positive were excluded. Mevalonic aciduria was clinically defined, along with 2 MVK mutations, by any of the following: severe psychomotor retardation, progressive cerebellar ataxia, typical dysmorphic features, or progressive visual impairment.

The physicians requesting the tests prospectively provided clinical data, using a questionnaire that inquired for the following characteristics of attacks: age at onset, duration, and clinical features (fever, lymphadenopathy, hepatosplenomegaly, abdominal pain, vomiting, diarrhea, joint pain, skin lesions).

**Derivation method.** Mutation-positive patients (2 mutated MVK alleles) were compared to mutation-negative patients with the Mann-Whitney and Fisher tests. All variables were entered in the recursive partitioning algorithm to find the most specific composite clinical criterion satisfied by all mutation-positive patients.

Step by step, the algorithm found the best variables (and best cutoff value for quantitative variables) to distinguish mutation-positive from mutation-negative patients. It was manually overridden when appropriate, to ensure clinical meaning and applicability of the classification rule. When 2 variables were close candidates at one step, several characteristics were taken into account to choose between them: robustness of the association between the variable and the mutation status (strong association in univariate analysis), reliability of the variable (objective measure), and number of missing values (threat to the validity of the association). During the derivation process, the imputation method for missing values was the best-case hypothesis: patients with missing values were allocated to the group they best fit into regarding the mutation status.

**Validation group.** The validation group consisted of all patients in whom genetic testing was performed from January 2004 until June 2007 in a single large tertiary care center. Genetic testing was ordered by or after consultation of an expert from the center but without prior measurement of mevalonic aciduria or MVK activity. The most prevalent mutations (Y377L, H20P, I268T) were first screened and if negative, the gene was completely sequenced. Patients displaying clinical features of mevalonic aciduria or with a family member who had already tested positive were excluded. Clinical data were extracted from the international HIDS database (University Medical Center St. Radboud; www.hids.net) in which data from patients with suspected and proven HIDS are collected.

**Validation method.** In the validation population, missing data were imputed according to the worst-case hypothesis: in mutation-negative patients, missing data were assigned to have a positive composite criterion if possible, and vice versa. Sensitivity, specificity, and negative likelihood ratio of the composite clinical criterion were assessed in the validation group. The potential influence of the rule was evaluated with the number of genetic tests that could have been avoided by using the composite criterion in the validation group to select patients for genetic testing.

Statistical analyses were performed with Stata 8.2 (Stata Corp.) and recursive partitioning with JMP 5.1 (SAS Institute).

**RESULTS**

**Patients.** The French derivation group included 149 patients with genetic testing, among whom 35 (23%) were mutation-positive. The Dutch validation group included 93 patients with genetic testing, among whom 28 (30%) were mutation-positive. Tested patients and mutation-positive patients were similar in the derivation and validation groups (Table 1). Characteristics of mutation-positive and mutation-negative patients in the derivation group are displayed in Table 2.

**Clinical criterion.** The composite criterion [onset age < 5 years old OR (joint pain during attacks AND length of attacks < 14 days)] was identified by recursive partitioning as the most specific among perfectly sensitive criteria. In other words, among all clinically meaningful criteria satisfied by all mutation-positive patients in the derivation group, the fewest mutation-negative patients satisfied this one.

According to the worst-case analysis in the validation group (Figure 1), the composite criterion had a sensitivity of 100% (95% CI 88% to 100%), a specificity of 28% (95% CI 17%–40%), and a negative likelihood ratio of 0 (95% CI 0–0.44). If genetic testing had been performed only in patients with a positive composite criterion, no mutation-positive patient would have been missed and 18 tests (19%) would have been avoided (Figure 1, unshaded boxes of the partition tree: 13 patients with onset age ≥ 5 years old and no joint pain during attacks; 5 patients with onset age ≥ 5 years old, with joint pain during attacks but with attacks lasting ≥ 14 days).

**DISCUSSION**

We present a clinical criterion that can prevent the use of unnecessary testing for MVK in patients with recurrent fever of unknown origin, without missing a single mutation-positive patient. Half of the tested and mutation-positive patients were adults at the time of genetic testing. This criterion can therefore be used in both pediatric and adult medicine.

We used recursive partitioning to derive the criterion. This hypothesis-free multivariable method natively explores interactions between predictor variables. It is also easy to understand by clinicians and well suited to find a criterion with maximal sensitivity, rather than a criterion that distinguishes positive and negative patients with maximal overall accuracy.

We choose to derive a perfectly sensitive criterion because clinicians are reluctant to use clinical prediction rules that might miss patients with disease. In return, the specificity is rather low: 28% in the validation set. However, this specificity is similar to that of other widely used perfectly sensitive clinical prediction rules devised to save resources. Moreover, we used worst-case imputation for missing values to estimate the specificity in the validation group; the true specificity is conceivably higher. The value of the criterion is likely to be further underestimated because the validation group underwent a triage by HIDS experts to exclude unlikely cases before genetic testing. Experts’ advice is subjective and unsystematic, but it is the best clinical filter currently available for HIDS. Our study provides an explicit criterion to prevent unnecessary genetic testing for HIDS, which has an added value even over experts’ advice.

Selecting patients for genetic testing is required, since previous research has shown that systematic genetic testing for HIDS in patients with recurrent fever has a very low
yield. In a group of 60 patients with recurrent fever and negative testing for the most likely autoinflammatory syndrome other than HIDS, not a single one was mutation-positive. In another study of patients with recurrent fever, negative testing for familial Mediterranean fever, and at least one of 3 features compatible with HIDS (aphthous ulcers, post-vaccination reactivity, cervical lymphadenopathy), only 2% were mutation-positive. Both these studies highlight the need for guidance to rationalize the ordering of genetic studies in patients with recurrent fever.

Clinical features of mutation-positive patients were close in both groups and very similar to the largest published series. Some features like joint pain, diarrhea, hepatosplenomegaly, or lymphadenopathy were more prominent during attacks in mutation-positive than in mutation-negative patients. However, no single clinical feature was perfectly sensitive and able by itself to exclude the diagnosis of HIDS when missing.

Although elevated serum IgD values were initially considered diagnostic, many patients with a compatible clinical picture and elevated IgD values were found to be mutation-negative when genetic testing became available. Further, it was recently shown that elevated serum IgD concentrations in patients with suspected HIDS have very poor positive and negative predictive values. Mandey, et al therefore proposed to use a more specific denomination — “mild mevalonate kinase deficiency” — instead of the historical name, hyperimmunoglobulin D syndrome, which puts a misleading emphasis on an inconstant and unspecific feature of the disease.

Urinary mevalonate concentrations are within the normal range in the majority of patients with HIDS between attacks.

Table 1. Comparison of the derivation (French) and validation (Dutch) groups. Results are given as median (interquartile range) or number of patients (percentage) and compared with the Mann-Whitney or Fisher tests.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Derivation Group, N = 149</th>
<th>Validation Group, N = 93</th>
<th>p</th>
<th>Derivation Group, N = 35</th>
<th>Validation Group, N = 28</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at genetic testing, yrs</td>
<td>113 (5–24)</td>
<td>35 (7–35)</td>
<td>0.06</td>
<td>99 (1.5–14)</td>
<td>35 (2.5–3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age at disease onset, yrs</td>
<td>91 (3–6.5)</td>
<td>31 (5–3.7)</td>
<td>0.22</td>
<td>103 (69–67)</td>
<td>35 (29–68)</td>
<td>0.03</td>
</tr>
<tr>
<td>Male (%)</td>
<td>114 (58–51)</td>
<td>35 (15–43)</td>
<td>0.44</td>
<td>104 (101–97)</td>
<td>34 (34–100)</td>
<td>0.43</td>
</tr>
<tr>
<td>Abdominal pain (%)</td>
<td>100 (72–72)</td>
<td>34 (28–82)</td>
<td>0.26</td>
<td>103 (69–67)</td>
<td>33 (29–88)</td>
<td>0.03</td>
</tr>
<tr>
<td>Joint pain (%)</td>
<td>95 (30–32)</td>
<td>35 (21–60)</td>
<td>0.004</td>
<td>33 (15–45)</td>
<td>18 (8–44)</td>
<td>1</td>
</tr>
<tr>
<td>Rash (%)</td>
<td>33 (15–45)</td>
<td>18 (8–44)</td>
<td>1</td>
<td>33 (15–45)</td>
<td>18 (8–44)</td>
<td>1</td>
</tr>
<tr>
<td>Hepatosplenomegaly (%)</td>
<td>86 (10–12)</td>
<td>33 (17–52)</td>
<td>&lt;0.001</td>
<td>86 (39–45)</td>
<td>30 (22–73)</td>
<td>0.01</td>
</tr>
<tr>
<td>Lymphadenopathy (%)</td>
<td>86 (39–45)</td>
<td>30 (22–73)</td>
<td>0.01</td>
<td>86 (39–45)</td>
<td>30 (22–73)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table 2. Comparison of mutation-negative and mutation-positive patients in the derivation (French) group. Results are given as median (interquartile range) and number of patients (percentage) and compared with the Mann-Whitney and Fisher tests.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Mutation-negative, N = 114</th>
<th>Mutation-positive, N = 35</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at genetic testing, yrs</td>
<td>113 (5–24)</td>
<td>35 (7–35)</td>
<td>0.06</td>
</tr>
<tr>
<td>Age at disease onset, yrs</td>
<td>99 (1.5–14)</td>
<td>35 (2.5–3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Length of attacks, days</td>
<td>91 (3–6.5)</td>
<td>31 (5–3.7)</td>
<td>0.22</td>
</tr>
<tr>
<td>Male (%)</td>
<td>114 (58–51)</td>
<td>35 (15–43)</td>
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and these patients, unlike patients with mevalonic aciduria, have only mildly elevated concentrations of urinary mevalonate during attacks. Measurement of urinary mevalonate concentration is therefore not sensitive enough to select patients before genetic testing for HIDS. MVK activity measurement should be the diagnostic “gold standard” for HIDS. However, it is very time-consuming and labor intensive, making it at least as costly as genetic testing. Moreover, radiometric assays are performed only in selected laboratories with adequate radioprotection measures.

Gattorno, et al. devised a diagnostic score to screen children with recurrent fever before genetic analysis for HIDS, familial Mediterranean fever, or tumor necrosis factor-receptor-associated periodic syndrome. The major strength of this score is to screen for genetic fevers as a whole, whereas we considered only HIDS. However, some drawbacks may limit its applicability. First, 90% of the patients in the derivation set were ≤ 18 years old at genetic testing. The proportion is not provided for the validation set, but must be quite close since the mean age at diagnosis was ≤ 10 years old. The diagnostic score must therefore be considered a pediatric tool, whereas children and adults were equally represented in our study. This is important because patients diagnosed in adulthood are likely to have milder or atypical forms of genetic fever. Second, the diagnostic score was negative in one patient with HIDS in the original validation set, indicating an imperfect sensitivity. In our derivation process, we put the highest value on a perfect sensitivity in order to guarantee access to genetic testing for all diseased patients. Third, the numbers of patients with HIDS in the derivation and validation sets were much smaller in the study by Gattorno, et al: 18 and 13 patients, respectively, compared to 35 and 28 in our study. Representativeness can hardly be guaranteed with such a small sample size. Unfortunately, we were unable to evaluate the diagnostic score on our patients because of missing data. However, we were able to evaluate the regression tree devised to select the first gene to be tested. The tree was able to identify 12/13 (92%) patients with HIDS in the original validation set, but only 13/28 (46%) in our validation group. These results are widely discrepant and question the external validity of the whole study by Gattorno, et al., at least in a mixed population of children and adults like ours.

Our study has some limitations. First, HIDS is a rare condition and both groups count a limited number of patients. Nevertheless, this is one of the largest clinical studies performed on HIDS to date. Second, because of the retrospective design of the study, many data were missing on several features. For example, data on aphtosis, pharyngitis, and reaction to vaccination were available for only 16, 15, and 12 mutation-positive patients, respectively, in the derivation group. These variables could not be included in our analysis because of a high risk of response bias. With complete data, we might have generated a classification rule with higher specificity and positive predictive value. Third, since the study was designed to evaluate when genetic testing for
MVK mutations has no value, we cannot recommend in which patients genetic testing should be considered. A prospective, preferably multicenter study with clear inclusion criteria is needed to assist clinicians deciding when to perform genetic testing for MVK or other gene mutations in patients with recurrent fever.

Genetic testing for HIDS can confidently be avoided in patients who had their first fever attack at age ≥ 5 years and whose attacks last more than 14 days or are not marked by joint pain.

REFERENCES