Joint Bone Spine 82 (2015) 240–244

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

Original article

A restrospective survey of patients's journey before the diagnosis of mevalonate kinase deficiency

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ARTICLE INFO

Article history:
Accepted 23 December 2014
Available online 9 February 2015

Keywords:
Mevalonate kinase deficiency
Hyper-IgD syndrome
Auto-inflammatory disease
Diagnosis
Disease burden

ABSTRACT

Mevalonate kinase deficiency (MKD) is an autosomic recessive auto-inflammatory disease caused by mutations of the *MVK* gene. MKD being a very rare disease, numerous misdiagnoses and medical referrals may precede the right diagnosis, amplifying the burden of the disease.
Objectives: To evaluate the patient's medical referrals between the first symptom and the diagnosis of MKD and the diagnosis delay.
Methods: A questionnaire was sent to French paediatric and adult rheumatologists to retrospectively collect information from genetically confirmed patients with MKD regarding the first symptoms of the disease, the different diagnoses made previously, the treatments received, and the disease burden evaluated mainly by the number of hospitalizations.
Results: Thirteen patients were analyzed. The mean age at onset was 9.5 months (birth to 36 months). The average diagnosis delay was 7.1 years. Eleven of them were hospitalized at least 5 times before the establishment of the diagnosis. A wide variety of diseases had been suspected: systemic juvenile idiopathic arthritis, periodic fever aphtous stomatitis pharyngitis adenitis syndrome, other hereditary recurrent fever, vasculitis, connective tissue disease, inflammatory bowel disease, gastritis, infections and immunodeficiency. Before the right diagnosis, 9 patients received corticosteroids and 6 patients received non-steroidal-anti-inflammatory drugs. Half patients had received repeated antibiotics, one third had received intravenous immunoglobulin, and the others were treated with immunosuppressive drugs or hydroxychloroquine.
Conclusions: MKD is a serious disease still difficult to treat, however earlier accurate medical referral and care, by increasing physicians' awareness, is critical to improve both the disease course and quality of life.

1. Introduction

Misdiagnosis and delayed diagnosis are frequent in rare diseases and can lead to morbidity though inappropriate procedures or treatments. Mevalonate kinase deficiency (MKD) is a rare autosomal recessive disease, which takes part of the spectrum of inherited auto-inflammatory diseases among which there is the group of hereditary recurrent fevers (HRF). It is caused by mutations in the *Mevalonate kinase* (*MVK)* gene responsible for reduced mevalonate kinase activity leading to overproduction of pro-inflammatory isoprenoids, reduced synthesis of cholesterol and accumulation of mevalonic acid in plasma and urine [1]. Two phenotypes of MKD are delineated according to the level of enzymatic deficiency; however, a wide spectrum of intermediate phenotypes has been reported [2]. The partial deficiency or hyperimmunoglobulin D syndrome (HIDS) is characterized by acute episode of high fever occurring every 4 to 6 weeks and lasting about 3 to 7 days frequently associated with digestive manifestations, oral ulcers and cervical lymphadenopathy. Other common symptoms include hepato-splenomegaly, headache, pharyngitis, arthralgia and skin rashes. The complete deficiency (< 1%) or mevalonic aciduria (MA) is a severe form, sometimes lethal in which ocular symptoms, neurologic symptoms, sensorial dysfunctions, failure to thrive, and dysmorphic features complete the classical signs of HIDS. First symptoms of MKD

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http://dx.doi.org/10.1016/j.jbspin.2014.12.011
1297-319X/

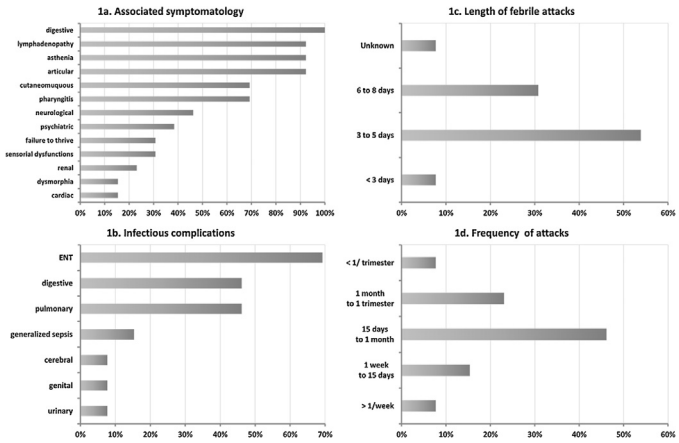

Fig. 1. Associated symptomatology (a), infectious complications (b), length of febrile attacks (c) and recurrence of attacks (d) in mevalonate kinase deficiency.

appear very early in life, usually within the first year [3], occasionally with severe neonatal hepatitis, but most patients will undergo an extensive workup before coming to the diagnosis sometimes many years later. The aim of this study is to describe the patient's medical referrals between the first symptom and the diagnosis of MKD, to evaluate the diagnosis delay, the iatrogenic harm caused by diagnosis errors and the disease burden in MKD patients.

2. Methods

In 2013, we sent a questionnaire via email or postal mail to 14 paediatric and adult rheumatologists, members of the French Paediatric Society for Paediatric Rheumatology (SOFREMIP) practicing in 10 French hospitals to retrospectively collect information from genetically confirmed MKD patients. All children or adults with an available clinical history of MKD and mutation in the *MVK* gene were included in the study. The questionnaire requested demographic details and information about age of onset of the disease, initial symptoms, evoked diagnoses, number of hospitalisations and treatments prescribed before the diagnosis and the diagnosis delay. Data were collected in medical reports and in hospitalization letters by the authors or the patient's referent doctor. In 3 cases, parents were contacted by phone to complete the data. Patients and caregivers gave their approval for publication of their medical information. In accordance with French regulations, no ethical committee was required for this retrospective study.

3. Results

Thirteen patients (7 girls and 6 boys) diagnosed with HIDS ($n = 11$) and MA ($n = 2$) between 1999 and 2013 were included. Their data are summarized in Table 1. Seven of them have already been reported in the literature [4–8], but the previous reports neither spot the diagnosis approach nor describe the delay for MKD final diagnosis. Twelve patients had two identified mutations in the *MVK* gene and one was heterozygous for the mutation (patient 13). The mean age at onset was 9.5 months (from birth to 36 months) in twelve cases and was unknown in one case (patient 10). Attacks of fever frequently associated with digestive, articular and cutaneo-mucous symptoms (Fig. 1a) lasted between 2 to 8 days with an average of 4 days (Fig. 1c) and had a variable frequency (Fig. 1d). Half of the children could predict the advent of attacks very shortly before a rise in body temperature: prodromal symptoms included constitutional signs (tiredness, backache, and headache) and psychological signs (irritability). In 10 patients, precipitating factors were found: febrile attacks were caused by viral infections (7 cases), vaccinations (8 cases) and stress (5 cases) (Table 1). The average diagnosis delay was 7.1 years (range 1–27 years) with a median of 3.8 years (standard deviation 7.48 years). Eight patients began the disease before 1999 with an average diagnosis delay of 10.2 years (range 1–27 years) whereas those born after 2000 had a mean diagnosis delay of 2.3 years (range 1–3.8 years). During all these years, many diagnoses were mentioned: systemic juvenile idiopathic arthritis (JIA) ($n = 6$); periodic fever aphtous stomatitis pharyngitis adenitis syndrome ($n = 2$); familial mediterranean fever ($n = 4$), chronic infantile neurological cutaneous and articular syndrome ($n = 1$); Kawasaki disease ($n = 2$), Henoch–Scholein purpura ($n = 2$); connective tissue disease ($n = 2$); gastritis ($n = 1$), inflammatory bowel disease ($n = 1$); recurrent viral infection ($n = 2$), acute resistant pyelonephritis ($n = 1$), maternal to foetal infection ($n = 2$); congenital malformation syndrome ($n = 1$) and immunodeficiency ($n = 1$). The accurate number of hospitalizations before diagnosis of MKD was not always available but 6 of 13 patients were hospitalized more than 10 times before the right diagnosis. Four patients (patient 1, 4, 11 and 12) were admitted more than 20 times before the right diagnosis. Two patients were hospitalized 8 and 9 times before diagnosis and four less than 5 times. Just one patient (patient 2) was never hospitalized. The duration of the stays ranged from 1 day to 9 months. Patients were hospitalized for fever of unknown origin or for infection (Fig. 1b). Patient 3 spent 5 months at hospital for a pneumococcal pleuro-pulmonary infection associated to influenza A, complicated by acute respiratory distress syndrome, pneumothorax and deep venous thrombosis. Five other patients had acute lobar pneumonia (#1, 5, 6, 7, 11). Gastrointestinal infections were common, such as *Salmonella* enteritis (#7, 11), pancreatitis (#9, 12) and ileocolitis (#5). Patient 12 had viral meningitis (#12). Finally, there were one case of orchitis (#2) and 1 case of non-complicated acute pyelonephritis. Patient 2 had three endoscopic exams (proctoscopy, colonoscopy and rhinoscopy) and five types of biopsy (skin, neuromuscular, liver, renal and jejunal). MKD was also associated with 3 cases of depression (patients 9, 10, 12), lack of socialization in one patient and hyperactive comportment in another one. Numerous treatments were administrated before diagnosis: antipyretic agents, repeated antibiotics ($n = 7$), corticosteroids ($n = 9$), colchicine ($n = 6$), intravenous immunoglobulins ($n = 4$), azathioprine ($n = 2$), cyclosporine, methotrexate, cyclophosphamide, hydroxycloroquine and infliximab therapies for suspicion of auto-immune disease.

4. Discussion

Errors in the management of MKD were common and resulted from failure in its diagnosis. In our patients, 14 different diagnoses were evoked before the right diagnosis and numerous ineffective treatments were given. All but one patient were hospitalized several times before diagnosis. In medicine, a significant portion of misdiagnosis arises because of inadequate knowledge, faulty data gathering and/or faulty verification. Misdiagnosis depends on the frequency of the disease, knowledge in the medical world and possibilities to diagnosis. MKD is very rare with a variable prevalence in Europe: about fifty cases of MKD in France and Belgium [7] and a prevalence < 1/1,000,000 in German children whereas 11% of HRF are MKD in Italia [9]. The first patients were described in 1984 [10] and the *MVK* gene mutations discovered in 1999 [11]. Many physicians are still unfamiliar with the disease leading to incorrect diagnoses, numerous and sometimes unnecessary hospitalizations, inappropriate and harmful therapeutic procedures. This ignorance of the disease has important impact for patients, parents and the health care system due to clinical, psychological, sociological and economic consequences. In our patients, the febrile attacks of unknown origin lead to multiply hospitalisations with several