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CASE REPORT

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A patient with hyper-IgD syndrome in Antalya, Turkey

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Abstract Hyper-IgD syndrome is a periodic fever syndrome that presents with recurrent episodes of high fever accompanied by lymphadenopathy, abdominal distress, arthralgias or arthritis, headache and skin lesions. The diagnosis is based on clinical grounds and elevated serum IgD levels (> 100 U/ml), but requires a high index of suspicion, and a mevalonate kinase enzyme defect. Most patients are from western Europe but there are others identified in other countries. We describe a 17-year-old patient who had been followed with the diagnosis of familial Mediterranean fever for a long time before she was diagnosed with hyper-IgD syndrome.

Keywords Familial Mediterranean fever · Hyper-IgD syndrome

Abbreviations *FMF* Familial Mediterranean fever · *HIDS* Hyperimmunoglobulinemia D and periodic fever syndrome

Introduction

Hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) is an autosomal recessive inflammatory disorder characterized by recurrent episodes of high fever accompanied by lymphadenopathy, abdominal distress (pain, vomiting, diarrhea), joint involvement (arthralgias/arthritis) and skin lesions (erythematosus macules and papules) [1, 2]. The attacks typically occur every 4–6 weeks and last 3–7 days, start early, and persist throughout life; between attacks patients are asymptomatic [3, 4]. Hyper-IgD syndrome is caused by mutations in the mevalonate kinase (MVK) gene, leading to MVK deficiency [5]. The pathogenesis remains unclear and the role of IgD in the pathogenesis remains to be elucidated [6]. The diagnosis is based on clinical grounds and continuously high serum IgD levels (> 100 U/ml) but requires a high index of suspicion and an MVK enzyme defect. The HIDS registry in Nijmegen, the Netherlands, currently has clinical data on 188 published and unpublished cases worldwide (information is available at http://www.hids.net). Most patients were white and from western European countries; approximately 60% were Dutch or French [7]. We describe a 17-year-old patient who had been followed with the diagnosis of familial Mediterranean fever (FMF) for a long time before she was diagnosed with HIDS. The main purpose of reporting this case was that FMF might not be the only reason for periodic fever in our region.

Case report

A 17-year-old Turkish girl who had been followed with the diagnosis of FMF was admitted to the Akdeniz University Hospital, Antalya, in March 2001 because of high fever, abdominal pain, arthralgia and headache. Her first symptoms started in early childhood and recurred every 2–3 months, lasting 3–5 days, and did not respond to colchicine therapy as well as would be expected. Family history for FMF was negative. On physical examination her blood pressure was 110/70 mmHg, pulse rate 100/min, respiration rate 16/min, and fever 39.0°C (axillary). Large lymphadenopathic nodules 1×1.5 cm were present bilaterally in the cervical region, and generalized abdominal tenderness was present. The rest of the physical examination was normal. Her laboratory analysis revealed a high white cell count $13.2\times10^3/mm^3$, (normal: $4.8–10.2\times10^3/mm^3$), 80% neutrophils; high erythrocyte sedimentation rate 40 mm/h (normal: 0–20 mm/h); high plasma fibrinogen level 687.30 mg/dl (normal: 180.0–350.0 mg/dl); high C-reactive protein 12 mg/dl (normal: 0.0–0.5 mg/dl); high serum IgD 374 IU/ml (normal: 20–99 IU/ml) and high serum IgA 402 IU/ml (checked three times normal: 68–378 IU/ml). Her last clinical attack took place while she was on colchicine 1.5 mg/day.

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Genetic analysis for FMF was performed, and heterozygosity with the M680I mutation in the MEFV gene was found. It was unfortunate that genetic analysis for MVK enzyme defect could not be performed. She was diagnosed with HIDS based on clinical symptoms, laboratory results and poor response to colchicine therapy.

Discussion

Hereditary periodic fever syndromes are a group of mendelian disorders defined by recurrent attacks of generalized inflammation for which no infectious or autoimmune cause can be identified [5, 8]. Two of these disorders, HIDS and FMF with periodic fever syndromes, are inherited as autosomal recessive traits but are different entities, epidemiologically, clinically and genetically [9, 10].

FMF is the most prevalent periodic fever syndrome, affecting more than 10,000 patients worldwide, predominantly people from the Mediterranean basin (including Turks, Sephardic Jews, Arabs and Armenians). Most patients with HIDS are white and are from western European countries, approximately 60% being Dutch or French [11]. There are clinical differences between HIDS and FMF, such as the lymphadenopathy, skin eruption and symmetry of arthritis in HIDS, and the occurrence of monoarthritis, peritonitis and pleurisy in FMF. Moreover, HIDS patients do not respond to colchicine [12].

Linkage studies indicate that the gene encoding for FMF is different from that for HIDS. Hyper-IgD syndrome is caused by mutations in the MVK gene (chromosome location 12q24), leading to MVK deficiency [13]. FMF is caused by mutations in the MEFV gene (chromosome location 16p13) [1, 5], but it is unfortunate that genetic analysis for MVK enzyme defect cannot yet be performed in our institution. Genetic analysis for FMF was done in this case and heterozygosity with the M680I mutation in the MEFV gene was found. Even though there are FMF cases reported with high serum IgD in the literature [14], the IgD level in our case was too high (347 IU/ml) to be considered as FMF. For this reason, based on both difficulty in controlling the clinical condition with colchicine and the very high serum IgD, we considered this case to be hyper-IgD syndrome. The possibility of FMF with very high IgD serum levels did not look feasible to us, as there are no reported cases in the literature.

We think that despite the higher rate of occurrence of FMF in our region, HIDS should be considered in patients with persistent attacks despite intense colchicine therapy. One should always consider the rarest possible diseases in the process of making a diagnosis.

References

1. Drenth JP, Denecker NE, Prieur AM, van der Meer JW (1995) Hyperimmunoglobulin D syndrome. Presse Med 24:1211–1213
2. Cuisset L (2001) Molecular analysis of MVK mutations and enzymatic activity in hyper-IgD and periodic fever syndrome. Eur J Hum Genet 9:260–266
3. Drenth JP, van Deuren M, van der Ven-Jongekrijg J, Schalkwijk CG, van der Meer JW (1995) Cytokine activation during attacks of the hyperimmunoglobulinemia D and periodic fever syndrome. Blood 85:3586–3593
4. Wauters IM, Linskens RK, Stehouwer CD (2000) Periodic fever due to hyper-IgD syndrome. Ned Tijdschr 144:809–811
5. McDermott MF, Frenkel J (2001) Hereditary periodic fever syndromes. Neth J Med 59:118–125
6. Scolozzi R (1995) Hyper-IgD syndrome (HIDS). Recenti Prog Med 86:243–247
7. Simon A, Cuisset L, Vincent MF et al. (2001) Molecular analysis of the mevalonate kinase gene in a cohort of patients with the hyper-igd and periodic fever syndrome: its application as a diagnostic tool. Ann Intern Med 135:338–343
8. Centola M, Aksentijevich I, Kastner DL (1998) The hereditary periodic fever syndromes: molecular analysis of a new family of inflammatory diseases. Hum Mol Genet 7:1581–1588
9. Livneh A, Drenth JP, Klasen IS et al. (1997) Familial Mediterranean fever and hyperimmunoglobulinemia D syndrome: two diseases with distinct clinical, serologic, and genetic features. J Rheumatol 24:1558–1563
10. Grateau G, Cuisset L, Dode C, Delpech M (2002) Hereditary intermittent fevers, other than familial Mediterranean fevers. Rev Prat 52:155–159
11. Drenth JP, Van der Meer JW (2001) Hereditary periodic fever. N Engl J Med 345:1748–1757
12. Samuels J, Aksentijevich I, Torosyan Y et al. (1998) Familial Mediterranean fever at the millennium. Clinical spectrum, ancient mutations, and a survey of 100 American referrals to the National Institues of Health. Medicine (Baltimore) 77:268–297
13. Drenth JP, Waterham HR, Kuis Wet al. (2000) Identification of the gene for hyper-IgD syndrome: a model of modern genetics. Ned Tijdschr Geneeskd 144:782–785
14. Medlej-Hashim M, Petit I, Adib S et al. (2001) Familial Mediterranean Fever: association of elevated IgD plasma levels with specific MEFV mutations. Eur J Hum Genet 9:849–854