Autoimmune manifestations in the clinical spectrum of haploinsufficiency A20: not to be confused with the diagnosis of Behçet

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❖ Introduction :

Studies published over 30 years ago suspected Mendelian genetic transmission in certain families affected at an early age by Behçet's disease.
The objective of this case series is to shed light on this rare but probably underdiagnosed autoinflammatory disease, associated with diagnostic wanderings lasting several years or even decade

❖ Method:

We report here the case of a French family with at least three members presenting HA20 and initially diagnosed early-onset Behçet's disease in our hospital.

❖ Results:

CASE 1: A 66 years old woman, clinical picture of a Behçet-like dating back to early childhood, presenting autoimmune hepatitis (HAI) in 2023 on liver biopsy, treated with steroid and Imurel for HAI with good evolution for the moment.

CASE 2: Her 47 years old daughter, with Behçet's like cutaneous-articular disease since the age of 6, presenting immunological thrombocytopenia in 2022(ITP). She received steroid for ITP with good response.

CASE 3: A 54 years old man, brother of case n°1, presenting with a picture of Behçet's disease revealed at an early age (10 years) associated with inflammatory colitis. In 2023, he developed multiple infectious complications: yersinosis, clostridial colitis and pneumopathy, resulting in a picture of immune deficiency. Anti-TNF treatment was offered to the patient in the event of a new digestive flare-up, and despite the advanced endoscopic lesions, he remains under regular, close surveillance.

HLAB51 antigen is absent in the family. Genetic analysis of the TNF/AIP3 gene revealed c.1880_1881 del variant on a single allele, resulting in the modification p.Cys627Phefs*44 in the amino acid chain of the A20 protein. This mutation, present in the heterozygous state in all 3 patients, points to autosomal dominant transmission of the disease.

❖ Discussion :

- A20 Haploinsufficiency (HA20) is a monogenic autoinflammatory disease associated with an autosomal dominant mutation in the TNFAIP3 gene. It induces a defect in the inactivation of the pro-inflammatory NF-kB pathway.(1)
- Compared to classic Behcet Disease , in a systematic review of 45 cases, the sex ratio is 1:2 with 15 men and 30 women respectively.(2)
- HA20 clinical hallmark is early onset aphtosis dominantly inherited. Febrile inflammatory outbreaks and joint involvement affect half of all patients, uveitis are rare, autoimmune conditions usually absent in Behçet disease can be seen (ITP, HAI, immune deficiency). Severe digestive disease is prominent, affecting more than 2/3 of cases and potentially severe and haemorragic (3).
- The first description of mutations in the TNF/AIP3 gene coding for the A20 protein involved in the TNF pathway was reported in 2016 by Zhou et al.(4) which 11 patients from 6 families with a new dominantly inherited autoinflammatory disease, termed haploinsufficiency of A20, characterized by childhood-onset episodic fevers, arthralgia/arthritis, oral and/or genital ulcers, skin pathergy, GI, and ocular inflammation .
- Berteau et al published the first French family of three members affected by early-onset Behcet's disease associated with a new mutation in the TNF/AIP3 gene (5).
- There was no standardised treatment in this HA20 cohort. The patients received various immunosuppressive drugs prior to the diagnosis of HA20; more recently, therapeutic approaches were guided by functional cytokine studies. Elevated levels of many proinflammatory cytokines (IL-1, TNF, IL-6, IL-18, IFNγ, IP-10) have been documented in patients with HA20.3 20 Anticytokine agents such as anti-TNF or anti-IL-1 have been effective in suppressing the systemic inflammation in most of our patients. Haematopoietic stem cell transplant might be considered in patients with severe and treatment-refractory disease(3).

❖ Conclusion :

The presence of a familial history of autoimmune or inflammatory manifestations outside the classical spectrum of Behçet's disease, as well as an early onset of symptoms, should alert the clinician. Early diagnosis of HA20 is key for identifying complications promptly and proposing the best treatment and follow-up strategy

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