'A20 haploinsufficiency (HA20): clinical phenotypes and disease course of patients with a newly recognised NF-kB-mediated autoinflammatory disease'

We have read with interest the article by Aeschlimann[1] and colleagues about clinical phenotypes and disease course of 16 American patients with A20 haploinsufficiency (HA20).

We would like to share our experience of a French family of three new related patients with juvenile onset Behçet's disease associated with HA20 (figure 1).

P1, a 48-year-old woman, was the first patient to be diagnosed with HA20 in July 2017 in our unit. She carries the heterozygous loss of function c.[994G>T] p.Glu332* truncating mutation, a mutation never described in the ovarian tumour domain of *TNFAIP3*. Since she was 6 years old, she had recurrent episodes of fever associated with bipolar ulcers, abdominal pain, hips and knees arthralgia, back pain, dry cough and asthenia. She was diagnosed with Behçet's disease in 2004 after a severe episode of abdominal pain with sigmoidal ulcers on colonoscopy. She also developed several anal fissures, two knee monarthritis, two lower limbs thrombophlebitis and one bilateral episcleritis. Laboratory tests showed polyclonal hypergammaglobulinaemia, elevated C reactive protein during episodes of fever and positive anti-neutrophil cytoplasmic antibodies (ANCA) without specificity.

She was initially treated with colchicine, partially and temporarily efficient. Non steroidal anti-inflammatories (NSAI) and corticosteroids were inefficient. On August 2017, we introduced a biotherapy, anti-interleukine 1 (anakinra 100 mg/day subcutaneously), which was very efficient in the first 2 weeks of treatment but was complicated by a pneumonia and lost efficacy afterwards. On October 2017, after a pneumococcal unconjugated vaccine dose, she developed high fever and a severe inflammatory swelling of the arm at site of injection that lasted 3 weeks (figure 2). She is currently receiving anti-TNFα (etanercept 25 mg/week) in association with colchicine, with moderate efficacy.

Concomitantly, her two children, P2 and P3, were diagnosed carriers of the same mutation in our unit in 2017.

P2, her 22-year-old son, had a history of recurrent fever, abdominal pain with diarrhoea and vomiting since he was 6 years old. He also developed oral recurrent ulcers and then

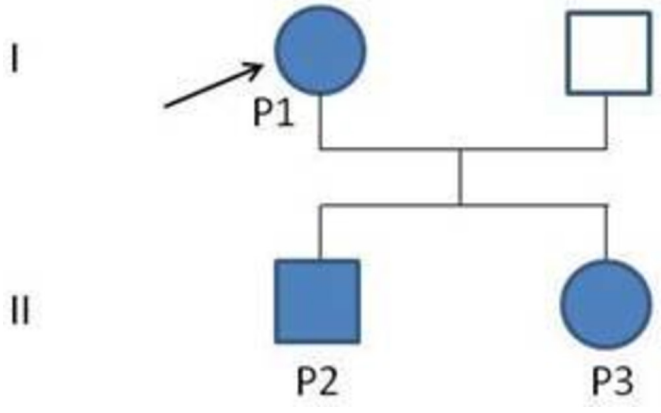

Figure 1 Pedigree of a French family diagnosed with HA20. The arrow indicates the proband. Filled in blue symbols indicate subjects carrying a p.Glu332* mutation in *TNFAIP3*. Men are indicated by squares, and women are indicated by circles.

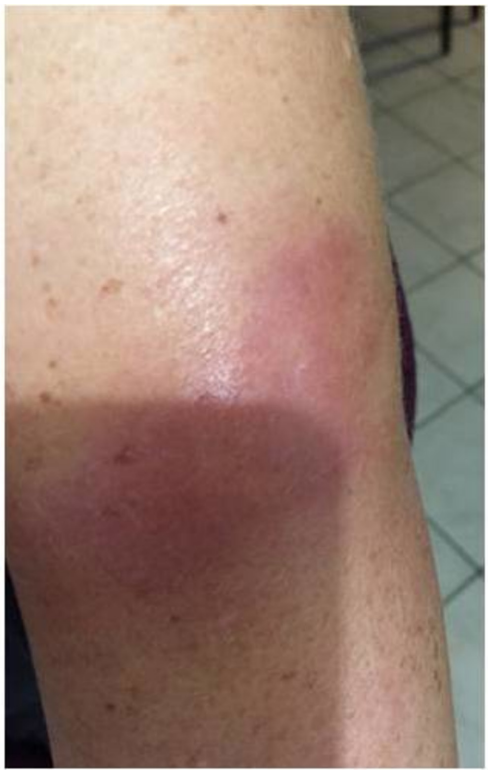

Figure 2 Photograph from the severe inflammatory swelling of the arm that occurred at site of pneumococcal unconjugated vaccine injection in patient P1.

a Hashimoto's thyroiditis and a vitiligo. He is currently treated with colchicine, with a good efficacy.

P3, her 15-year-old daughter, was diagnosed with Behçet's disease when she was 6 months old on bipolar ulcers associated with digestive disorders (abdominal pain, diarrhoea, vomiting and rectal bleeding). She also had recurrent fever, knees and hands arthralgia, several arthritis, pseudofolliculitis, urticaria and recurrent pharyngitis. She is currently treated with colchicine and mesalazine, with a good efficacy.

The family illustrates the common clinical features of this Behçet-like genetic autosomal dominant disorder recently described in association with *TNFAIP3* mutation, that is, recurrent oral and genital ulcers, digestive disorders, arthralgia/arthritis and recurrent fever starting in early childhood. Autoimmune disorders can coexist as in patient P2. Evolution of the disease is inconstant and unpredictable. Response to colchicine is inconstant and pharmacological control of inflammatory disorders can be tricky, as in patient P1.

Patients presenting with Behçet-like disease starting in early childhood, especially if there is a family history of similar symptoms, should be screened for *TNFAIP3* mutation, as clinical course and response to treatment in this genetic disorder differ from common Behçet's disease.

Florian Berteau,[1] Bénédicte Rouvière,[1] Alice Nau,[1] Rozenn Le Berre,[1,2] Guillaume Sarrabay,[3,4] Isabelle Touitou,[3,4] Claire de Moreuil[1,5]

[1]Département de médecine interne et pneumologie, CHU de Brest, Hôpital La Cavale Blanche, Brest, France
[2]EA 3882 – Laboratoire Universitaire de Biodiversité et Ecologie Microbienne (LUBEM), Groupe de Bactériologie-Virologie, Faculté de Médecine et des Sciences de la Santé, Université Bretagne Loire, Brest, France
[3]Cellules souches, plasticité cellulaire, médecine régénératrice et immunothérapies, INSERM, Univ Montpellier, Montpellier, France
[4]Département de génétique médicale, maladies rares et médecine personnalisée, CHU Montpellier, Montpellier, France

[5]EA 3878, GETBO, Université Bretagne Loire, Brest, France

Correspondence to Dr Claire de Moreuil, Département de médecine interne et pneumologie, CHU de Brest, Hôpital La Cavale Blanche, Brest 34295, France; claire.demoreuil@chu-brest.fr

Contributors All authors have contributed to the writing and to the corrections of this article.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Berteau F, Rouvière B, Nau A, *et al*. *Ann Rheum Dis* 2019;**78**:e35.

Received 3 March 2018
Accepted 5 March 2018
Published Online First 16 March 2018

► http://dx.doi.org/10.1136/annrheumdis-2018-213359

Ann Rheum Dis 2019;**78**:e35. doi:10.1136/annrheumdis-2018-213347

REFERENCE

1 Aeschlimann FA, Batu ED, Canna SW, *et al*. A20 haploinsufficiency (HA20): clinical phenotypes and disease course of patients with a newly recognised NF-kB-mediated autoinflammatory disease. *Ann Rheum Dis* 2018;77:728–35.