Do we need the PFAPA syndrome in adults with non-monogenic periodic fevers?

We read with great interest the article by Gattorno *et al* proposing a new set of criteria for the classification of autoinflammatory recurrent fevers.[1] This year's Paediatric Rheumatology INternational Trials Organisation(PRINTO) criteria are the third set of criteria for periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome in 3 years.[1–3] While these three different sets share common points, they also include distinct clinical features, thus resulting in discrepancies in the classification of patients.

To illustrate this issue, we report the clinical characteristics of a cohort of 34 consecutive adult patients (see table 1) followed in our centre between 2010 and 2018, and diagnosed with PFAPA based on the modified Marshall's criteria[4] (available as online supplementary material) with the exclusion of age at onset. Within this cohort, we sorted patients according to whether they did or did not meet one of the three sets of classification criteria (ie, Cantarini 2017, Vanoni 2018 and the PRINTO 2019 criteria available as online supplementary material). For Vanoni's criteria, we did not apply the age criterion. Regarding treatment response, we defined partial response as a clinically significant decrease in either the duration, the frequency or the intensity of flares as assessed by the treating physician. Complete response was defined as absence of flare. Of our 34 patients, 6 met Cantarini's criteria (designed specifically for adult-onset PFAPA), 17 met Vanoni's criteria, 13 met the PRINTO 2019 criteria and 13 did not meet any of the recent classification criteria for PFAPA (see online supplementary figure 1). Thirty-two (94%) patients had undergone genetic testing based on their specific characteristics, which all yielded inconclusive results. Regardless of the set of criteria fulfilled, our patients displayed globally similar therapeutic response and disease course. None developed AA amyloidosis. Most patients managed their flares using short courses of oral corticosteroids. Furthermore, long-term treatment with colchicine was successful in approximately 50% of patients (partial or complete response rate ranging from 43% to 76%). During follow-up, spontaneous remission or decrease in the duration, frequency or intensity of flares occurred in 50% of

Table 1 Patients' characteristics and therapeutic response according to the set of criteria fulfilled

	Overall (n=34)	Cantarini's criteria (n=6)	Vanoni's criteria (n=17)	PRINTO 2019 criteria (n=13)	Not classified* (n=13)
Female/male	23/11	4/2	12/5	8/5	9/4
Age at onset (years)	5.0 (2.4–15.8)	21.5 (15.8–25.3)	5.0 (1.5–9.0)	2.5 (0.65–5.0)	7.0 (4.5–16.0)
PFAPA duration (years)	16.4 (10.0–20.4)	4.5 (3.8–5.8)	14.9 (6.8–18.2)	16.4 (12.5–19.4)	18.6 (12.5–20.5)
Annual frequency of flares before start of therapy	12.0 (6.5–12.0)	10.0 (5.8–12.0)	12.0 (10.0–12.0)	12.0 (9.3–14.8)	8.3 (3.3–12.0)
Length of flares before start of therapy (days)	3.8 (3.0–4.6)	4.0 (3.9–4.8)	4.0 (3.3–4.6)	4.3 (3.3–5.1)	3.0 (2.6–3.5)
CRP during flares (mg/L)	113 (53–150)	152 (59–201)	104 (57–140)	111 (60–144)	67 (38–128)
Acute treatment of flares					
NSAID (n)	7	0	5	4	1
Corticosteroids (n)	24	5	13	11	8
Anakinra (n)	5	3	3	2	1
Long-term treatment					
Colchicine (n)	29	5	14	10	12
CR (%)	19	0	9	14	38
PR (%)	38	50	36	29	38
NR (%)	29	50	27	43	13
AE (%)	19	0	27	14	13
Anakinra (n)	1	0	1	0	0
CR (%)	100	–	100	–	–
PR (%)	0	–	0	–	–
NR (%)	0	–	0	–	–
Canakinumab (n)	1	1	0	0	0
CR (%)	0	0	–	–	–
PR (%)	0	0	–	–	–
NR (%)	100	100	–	–	–
Tonsillectomy/ adenoidectomy (n)	11	1	6	4	4
CR/PR (%)	27	0	17	25	50
NR (%)	73	100	83	75	50
Outcome at last follow-up					
CR/PR with no treatment (%)	50	40	56	67	40

Continuous variables are given in median (IQR).
*Patients fulfilling only modified Marshall's criteria.
AE, adverse effect leading to discontinuation; CR, complete response;CRP, C-reactive protein; NR, no response; NSAID, nonsteroidal anti-inflammatory drug;PFAPA, periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis; PR, partial response.

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patients (partial or complete remission rate ranging from 40% to 67%). Of note, as previously reported in adult PFAPA, tonsillectomy and/or adenoidectomy was inefficient in the majority.[5] Although the size of the cohort was insufficient to perform statistical tests, it seems that regardless of the set of PFAPA criteria used, the disease course and therapeutic response were identical in the four criteria set groups. As a result, recent attempts to diagnose PFAPA more accurately may not translate into the identification of distinct patient profiles in terms of disease course and therapeutic management. Moreover, the recently described heterogeneous group of undefined systemic autoinflammatory diseases (USAID), defined as recurrent inflammation not corresponding to the clinical picture of any well-defined SAID or without pathogenic mutation causing a known hereditary SAID, seems to display similar characteristics.[6] Therefore, the relevance of positioning PFAPA as a distinct entity than USAID in adult patients with non-monogenic periodic fevers is questionable.

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