

**Case Report**

Homeopathic Treatment of Children Suffering from PFAPA: A Retrospective Case Series

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Abstract

Introduction: Periodic Fever, Aphthous stomatitis, Pharyngitis, cervical Adenitis (PFAPA) syndrome is an acquired auto inflammatory disorder, frequently diagnosed in young children. Fevers recurring every three to eight weeks are the signature symptom. The aim of this retrospective case series is to present the course of disease during individualized homeopathic treatment in children suffering from PFAPA.

Case presentations: We collected the history and symptoms from 10 out of 13 (76.9%) consecutively treated PFAPA patients (5 girls) with a median age of 3.5 years [Q1-Q3: 3.1-4.4]. Clinical outcome was assessed using the “Modified NARANJO Criteria for Homeopathy-causal attribution inventory” (MONARCH range: -3 to 13 points: ≥ 8 points = presumable correlation between homeopathic therapy and improved symptoms or cure). We also described the individually chosen Homeopathic Medicinal Products (HMPs: n=21) used.

Results: All but one patient (MONARCH ≥ 8 points in 90%: 8 points: n=5; 9 points: n=3; 10 points: n=1; -2 points: n=1) recovered within one to five months of treatment. Median Follow up was 35.5 months [33.3-41.8]. A median of 4 HMPs [3-5] were applied to treat PFAPA (median fever 40°C [40.0-40.8]) mostly using Atropa Belladonna CH200 (100%), Calcium carbonicum CH200 (50%), Mercurius solubilis LM6/12 (40%), Phosphorus CH12/200 (40%) and Pulsatilla pratensis LM6/12 (30%). There was a time-dependent improvement with regard to frequency of flares, as well as intensity of symptoms, up to complete disappearance of disease. Some parents reported that physical improvement seemed to be accompanied by developmental behavioural leap.

Conclusions: This case series suggests that individualized homeopathy is a potential therapy option in patients with PFAPA.

Keywords: PFAPA; Periodic Fever; Homeopathy.

Abbreviations: PFAPA: Periodic Fever, Aphthous stomatitis, Pharyngitis, cervical Adenitis; HMP: Homeopathic Medicinal Product; SAID: Systemic Auto inflammatory Disease; HRF: Hereditary Recurrent Fever; CIM: Complementary and Integrative Medicine; CTCAE: Common Terminology Criteria for Adverse Events; ENT: Ear, Nose and Throat specialist; CRP: C-Reactive Protein; RSV: human Respiratory Syncytial Virus; MEFV: familial Mediterranean Fever Virus; CTP: Consensus Treatment Plan; CARRA: Childhood Arthritis and Rheumatology Research Alliance.

Introduction

During the last 20 years, the discovery of the inflammasome and the related genes of the systemic auto inflammatory diseases (SAIDs) have led to a completely new line of research [1]. SAIDs are caused by exaggerated activation of the innate immune system, in the absence of high-titer autoantibodies or antigen-specific T-cells [2]. Periodic fevers are characterized by inflammatory flares separated by intervals of general overall well-being. Hereditary recurrent fever (HRF) syndromes are genetic disorders secondary to mutations in genes involved in the innate immune response. A number of classification or diagnostic criteria have been developed in the past. Overall, these criteria lack accuracy and do not consider the results of genetic analyses, now an essential tool for the accurate diagnosis and classification of HRF [1].

Fevers recurring at a nearly predictable interval every three to eight weeks are the signature symptom of periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome. PFAPA syndrome is an acquired auto inflammatory disorder, which recurs in association with at least one sign of aphthous stomatitis, pharyngitis, and cervical lymph node enlargement, without clinical signs related to upper respiratory airway or other localized infections [3]. The disease usually has a rather benign course, although it might relapse during adulthood after a spontaneous or treatment-induced resolution in childhood.

The number of treatment choices currently available for PFAPA syndrome has grown in recent years, but data from clinical trials dedicated to this disorder is limited to small cohorts of patients or single case reports. The response of PFAPA patients to a single dose of corticosteroids is usually striking yet short-lived, while little data exist for treatment with cimetidine and colchicine's [3].

PFAPA syndrome was first described forty years ago and is probably the most frequent and least recognized cause of non-infectious recurrent fevers in children [3,4]. PFAPA should be considered in the absence of additional symptoms of abdominal pain, joint pain/swelling, and occasional skin rashes [5].

Homeopathy, one of the most popular complementary and

integrative medicine (CIM) disciplines, is based on the 'law of similar', which states that homoeopathically prepared substances causing symptoms in healthy individuals can be used to stimulate the healing process in patients who have similar symptoms due to their illness [6].

One of the authors (M.F.) has noticed a good response of PFAPA patients to homeopathic treatment. Therefore, he treated a series of children suffering from PFAPA with individualized homeopathy. The aim of the paper is to give an insight into homeopathic treatment of children suffering from PFAPA.

Methods

Participants

All authors confirm that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. The manuscript is in line with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals and aimed for the inclusion of representative human populations (sex, age and ethnicity) as per those recommendations. The study was approved by the Ethical Committee of the Sigmund Freud Private University, Vienna, Austria (Ethics Committee Application No. 803-2023) as of July 6, 2023; ClinicalTrials.gov Identifier: NCT05995288. Informed consent and assent were obtained from the parents, before commencing retrospective study procedures.

All children suffering from periodic fever with at least one of the symptoms of PFAPA besides fever, for at least 6 months, ages ranging from one to ten years, females and males were treated in the office of one of the authors (M.F.) with forty years' experience in individualized homeopathy, with a homeopathic diploma from the Austrian Medical Association. Children with treatment beginning between May 1, 2019, and December 31, 2020, were consecutively screened for this retrospective case series.

Homeopathic case taking and Homeopathic medicinal products (HMPs)

In individualized homeopathy, treatment consists of two main elements: taking the individual case history and prescribing individually selected HMPs, which correspond to the sum of symptoms presented by the patient. The purpose of the homeopathic case history is to ascertain the totality of signs and symptoms of the patient, enabling the selection of an individualized HMP based on the broad themes and idiosyncratic characteristics elicited from the totality of presenting symptoms: physical, mental and emotional [6,7]. Classical homeopaths generally use one HMP at a time, usually highly diluted and succussed, and in rare repetitions. HMPs were manufactured by Remedia, Eisenstadt, and by Schwabe Austria, Vienna, and both Austria. All HMPs are registered

according to the EU Directive 2001/83 and prepared according to the instructions of the European Pharmacopoeia [8,9]. During this preparation, HMPs are highly diluted and succussed, resulting in so-called homeopathic “potencies.” All HMPs were prescribed as globules, and there was no restriction on the HMPs and potencies used. The HMPs were administered orally. Five globules were administered sublingually where they dissolved.

Adverse Events

All patients were asked about adverse events at each follow-up visit according to the Common Terminology Criteria for Adverse Events (CTCAE). In addition, patients were asked to report suspected adverse events, homeopathic aggravations, the appearance of old or new symptoms, etc. to the homeopathic physician without delay. Opposite to adverse effects, homeopathic aggravation is an expected, mild, transient increase in pre-existing signs or symptoms that occur shortly after HMP administration, resolve quickly, and are associated with improvements in clinical complaints and/or general health [11].

Assessment of the modified Naranjo criteria

Case reporting follows the HOM-CASE guidelines respectively the guideline by Teut et al [11,12]. The modified Naranjo criteria were assessed post hoc by all authors. Discrepancies were clarified in a face-to-face interview. Clinical outcome of case reports was assessed using the “Modified Naranjo Criteria for Homeopathy-Causal Attribution Inventory” (Table 1) [13]. MONARCH score

ranges from -3 to 13 points; ≥ 8 points indicate presumable correlation between homeopathic therapy and improved symptoms or cure in chronic cases [13].

Results

During the study period, 13 children were screened. In the following paper, we present 10 case reports in detail; three case reports had to be excluded: in two cases, parents refused informed consent, despite anonymous reporting; in another case, parents could not be reached. If not otherwise stated, all described patients did not exhibit diarrhea, skin eruptions, joint pains, and/or chest pain during PFAPA, therefore excluding other periodic fever syndromes. We collected the history and symptoms from 10 out of 13 (76.9%) treated PFAPA patients (5 girls) with a median age of 3.5 years [Q1-Q3: 3.1-4.4]. All but one patient recovered within one to five months of treatment (MONARCH ≥ 8 points in 90%; 8 points: n=5; 9 points: n=3; 10 points: n=1; -2 points: n=1; Table 2). Median follow-up was 35.5 months [33.3-41.8]. Frequency of PFAPA symptoms in the reported cases are shown in Table 3: Periodic fever (10), aphthae (6), pharyngitis (9), and cervical adenitis (9). We also described the individually chosen HMPs (n=21) used (Table 4). A median of 4 HMPs [3-5] were applied to treat PFAPA (median fever 40°C [40.0-40.8]) mostly using Atropa Belladonna CH200 (100%), Calcium carbonicum CH200 (50%), Mercurius solubilis LM6/12 (40%), Phosphorus CH12/200 (40%) and Pulsatilla pratensis LM6/12 (30%). No adverse events attributable to the homeopathic treatment were reported.

	Yes	No	Not Sure or N/A
1. Was there an improvement in the main symptom or condition for which the homeopathic medicine was prescribed?	+2	-1	0
2. Did the clinical improvement occur within a plausible timeframe relative to the drug intake?	+1	-2	0
3. Was there a homeopathic aggravation* of symptoms?	+1	0	0
4. Did the effect encompass more than the main symptom or condition (i.e., were other symptoms, not related to the main presenting complaint, improved or changed)?	+1	0	0
5. Did overall well-being improve? (Suggest using a validated scale or mention about changes in physical, emotional, and behavioral elements)	+1	0	0
6 (A) <i>Direction of cure</i> : did some symptoms improve in the opposite order of the development of symptoms of the disease?	+1	0	0
6 (B) <i>Direction of cure</i> : did <i>at least one</i> of the following aspects apply to the order of improvement of symptoms: - from organs of more importance to those of less importance - from deeper to more superficial aspects of the individual - from the top downwards	+1	0	0

7. Did "old symptoms" (defined as non-seasonal and non-cyclical symptoms that were previously thought to have resolved) reappear temporarily during the course of improvement?	+1	0	0			
8. Are there alternative causes (other than the medicine) that –with a high probability- could have produced the improvement? (Consider known course of disease, other forms of treatment, and other clinically relevant interventions)	-3	+1	0			
9. Was the health improvement confirmed by any objective evidence**? (e.g., investigations, clinical examination,etc.)	+2	0	0			
10. Did repeat dosing, if conducted, create similar clinical improvement?	+1	0	0			
TOTAL SCORE	(range -3 to +13)					
* Homeopathic aggravation: A temporary worsening of pre-existing symptom(s) within a plausible timeframe after the administration a homeopathic medicine, followed by an improvement in the patient's condition.						
** Objective evidence: Findings that reflect expert external observation of any measurement of the patient. Objective evidence includes lab tests, X-ray reports, health care provider examination or observation, or other similar data						

Table 1: Modified NARANJO Causality Attribution Criteria. Patient (initials/brief descriptor).

Pat.	1	2	3	4	5	6	7	8	9	10
1	+2	+2	+2	+2	+2	+2	+2	+2	-1	+2
2	+1	+1	+1	+1	+1	+1	+1	+1	-2	+1
3	0	0	0	0	0	0	+1	+1	0	+1
4	0	0	0	0	0	+1	+1	0	0	0
5	+1	+1	+1	+1	+1	+1	+1	+1	+1	+1
6 A	0	0	0	0	0	+1	0	0	0	0
6 B	0	0	0	0	0	0	0	0	0	0
7	0	0	+1	0	0	0	0	0	0	0
8	+1	+1	+1	+1	+1	+1	+1	+1	0	+1
9	+2	+2	+2	+2	+2	+2	+2	+2	0	+2
10	+1	+1	0	+1	+1	+1	0	+1	0	+1
Total	+8	+8	+8	+8	+8	+10	+9	+9	-2	+9

Table 2: Modified NARANJO Causality Attribution Criteria for the 10 patients. Pat.: Patient Code No.; Total: Total Score.

Case	Periodic fever	Aphthae	Pharyngitis	Cervical Adenitis
1	X	0	X	X
2	X	0	X	X
3	X	X	X	0
4*				
5	X	X	X	X
6*				
7	X	0	0	X
8**				
9	X	X	X	X
10	X	X	X	X

11	X	X	X	X
12	X	0	X	X
13	X	X	X	X
Frequency	10	6	9	9

Table 3: Frequency of PFAPA symptoms in cases 1 to 10.

Atropa belladonna CH200 (10)
Calcium carbonicum CH200 (5)
Phosphorus CH200 (3)
Mercurius solubilis LM6 (2)
Mercurius solubilis LM12 (2)
Natrium muriaticum LM6 (2)
Pulsatilla pratensis LM6 (2)
Alumina CH12 (1)
Apis mellifica CH12 (1)
Arsenicum album CH200 (1)
China CH6 (1)
Eupatorium perfoliatum CH12 (1)
Influenzinum CH200 (1)
Ipecacuanha CH12 (1)
Lachesis CH200 (1)
Lycopersium esculentum CH12 (1)
Lycopodium clavatum CH30 (1)
Lycopodium clavatum CH200 (1)
Natrium sulphuricum CH12 (1)
Nux vomica LM6 (1)
Phosphorus CH12 (1)
Pulsatilla pratensis CH12 (1)
Sulfur LM6 (1)
Thuja CH12 (1)
Valeriana officinalis CH12 (1)

Table 4: Homeopathic medicinal products (HMPs) used sorted by frequency (in parenthesis) per patient.

Treatment(CONSORT item number)	Description	Reported on page number
Rational (2)	Type of homeopathy Individualized (aka classical, constitutional)	6
	Evidence base Sources, references	35,36

Participants (3)	Knowledge condition	6
	Baseline health definition in provings	
Medications (4)	Manufacture Manufacturer, Pharmacopoeia (or references process),	7,7
	Potency and scale	Potencies reported with each case report; Table 4
	Dilution method	-
	Nomenclature	
	Individualized: list or frequency table	Table 4
	Formula: constituents, trade name	
	Dosage	
Consultations (4)	Dose, timing, form	With all patients
	Setting	6
	Clinical history detail	With all patients
	Duration, frequency	With all patients
	Number needed to agree prescription	-
	Group process or expert consultation	-
Practitioners (4)	Confidence in prescriptions	-
	Number in study	1
	Experience, accreditation, qualifications	6
Co-interventions (4)	Current schools or styles of homeopathy	Hahnemann, Kent
	Included	
	Rationale, intended effect, references	-
	Duration, frequency	-
	Excluded	
	Stopping of mainstream interventions	-
Control interventions (4)	Antidotes	-
		-
Adverse Events (19)		0

RedHot - Checklist for reporting data on homeopathic treatments. The page numbers refer to the submitted manuscript

Case Presentations

Case 1

At the anamnesis in July 2019, the boy was four years and six months old. The child was breastfed for a year with extreme digestive problems with alternating diarrhea and constipation; digestion normalized when breastfeeding ended. The parents were divorced in October 2018. The boy was regarded to be highly sensitive; he spoke very well. Before worrisome events, he asked "What can happen then?". He was shy, reserved, not a daredevil.

Half a year ago at the age of four, the patient had mononucleosis. The right cervical lymph nodes were swollen, with enlarged axillary and inguinal lymph nodes on both sides, and splenomegaly. At that time, he was given *Lycopodium clavatum* by another homeopath.

First symptoms of PFAPA appeared at the age of twelve months: every five to six weeks he had a fever of up to 40.9°C for a week. Antipyretics were given very rarely. PFAPA was diagnosed by the pediatrician. For eight months, beginning when the boy was three years and ten months old, he had fever of up to 40.9°C every three weeks lasting for a week. He slept a lot, was very calm; up to 40°C he was not aggressive. The PFAPA episodes had a rapid onset and termination. With fever, the patient had a red face, a sore throat and swollen cervical lymph nodes on the left. There was no sensitivity to light or noise; now and then he had headaches; he had warm hands, but no aphthous ulcers. Two weeks ago, the boy had a fever of 40.7°C for six days while on vacation in Italy. With Betnesol® 0.5 mg (Betamethason, Alfasigma Schweiz AG, Zofingen, Switzerland) the fever disappeared for one day and vomiting occurred the next day; he would otherwise not vomit during a fever episode.

The homeopathic therapy consisted of *Atropa belladonna* CH200, once a week for four weeks, with the rapid onset and sudden end of the fever being the decisive factor in the choice of the HMP. The first dose of *Atropa belladonna* CH200 was given during fever, which subsided within 24 h. Upon reoccurrence of fever three days later the *Atropa belladonna* CH200 was repeated and acted again therapeutically. *Atropa belladonna* CH200 helped again when fever reoccurred after three more days.

The patient was highly sensitive. After the divorce of his parents, he experienced grief, and immediately following the divorce, the interval between the fever attacks shortened from five to three weeks. Taking this into account, the patient, now four years and seven months old, next received *Natrium muriaticum* LM6, five globules per day for three weeks. His craving for salty food confirmed the choice of *Natrium muriaticum*.

1. Follow-up three months after the first medical history taking: The parents reported that the boy had shown no more fever and he was in a good mood. The pediatrician could not find signs of

PFAPA anymore.

2. Follow-up six months and 44 months after the first medical history taking: the mother reported that her son had since been completely healthy and had no more fever attacks since the treatment with *Natrium muriaticum* LM6.

Case 2

At the anamnesis in October 2019, the male patient was seven years and six months old. The boy had been suffering from adenoids and tough, thick green-yellow nasal secretions since he was two years old. The patient had been suffering from attacks of fever with temperatures of up to 39.5°C every four weeks for 14 months. The fever lasted three days, and streptococcal angina had once been diagnosed four months ago. He had pain when swallowing during the fever. Furthermore, large tonsils and pharyngitis were noticeable, the cervical lymph nodes were slightly enlarged on both sides, aphthous ulcers did not appear. Headache sometimes occurred after the fever. PFAPA was diagnosed by the pediatrician. Because of the high and sudden fever, the patient was given *Atropa belladonna* CH200, five globules, once a week for four weeks. Because of the adenoids and the enlarged cervical lymph nodes, he next received *Calcium carbonicum* CH200 in the same dosage.

1. Follow-up four months after the first medical history taking: The parents reported that no more fever attacks had appeared.

2. Follow-up 17 months after the first medical history taking: The patient had no more fever attacks since treatment; only the tonsils were still slightly enlarged, though smaller than at the beginning of the treatment.

3. Follow-up 41 months after the first medical history taking: The boy was now completely healthy; the size of the tonsils was now normal. He was even tempered; the pediatrician, too, could not find any signs of PFAPA.

Case 3

The girl was three years old at the time of the first anamnesis in May 2019. Previous illnesses included bronchitis, pneumonia, otitis media (side is unknown) and urinary tract infections. The girl also often suffered from colds. PFAPA started around the age of 12 months; at 18 months, the PFAPA was definitely noticed and documented. Every three to four weeks there was a fever of up to 40°C, lasting for two to three days. There were also aphthae and an inflamed throat, but no enlarged lymph nodes. At the time of the initial anamnesis, the patient was at the ear, nose and throat (ENT) specialist who found enlarged tonsils and polyps. Two weeks prior, the girl had pneumonia, the localization was unclear; an X-ray was not taken. Therapeutically, she was given antibiotics and antipyretic drugs. A week prior, she had a fever and was given a prednisolone suppository in the children's hospital where the diagnosis PFAPA was made. The child was in a good mood, not aggressive, rather

funny and bright. Because of the previous pneumonia, the patient received five globules Phosphorus CH200 as the first HMP. Her appearance was also like an actress, a symptom pointing to Phosphorus; there were no further indicating symptoms.

1. Follow-up two months after the first medical history taking: Six weeks after the first case taking a fever of up to 39°C occurred. After consultation, the girl was given five globules of Atropa belladonna CH200, the decisive factor was the sudden onset of the fever. The fever went away within a short time on the same day without antibiotics or antipyretics.

In order to prevent pneumonia, the patient again received five globules of Phosphorus CH200 two months after first anamnesis. After a further week the fever came back, therefore the girl received three times five globules of Atropa belladonna CH200. In addition, the mother gave Nureflex® 20mg/ml oral suspension (Ibuprofen, Reckitt Benckiser Austria GmbH, Vienna, Austria) three times five ml within the same 24 hours. The fever disappeared within a day, the PFAPA episodes typically lasted two to three days with Nureflex® as only medicine. Three weeks later temperature was 37.8°C in the morning, which disappeared in the afternoon without any therapy. Her preference for eggs now reappeared, as well as her abdominal distension, and it was decided to prescribe five globules of Calcium carbonicum CH200 every two weeks for two months. Because of snoring, China officinal is CH6 followed five globules per day for three weeks. The repertorization revealed Calcium carbonicum regarding snoring; and China officinal is regarding snoring in children. Repertorization is used to determine the appropriate HMP by comparing symptoms, which are arranged according to a head-to-toe scheme by rubric.

2. Follow-up five months after the first medical history taking: There had been no fever since the last time two months ago. Her parents spontaneously reported a huge development spurt, and she now slept through the night without snoring; before she often woke up between 10 p.m. and midnight.

3. Follow-up 19 months after the first medical history taking: No fever attacks had occurred in the meantime. She was doing very well overall, and the enlarged tonsils had receded. No signs of PFAPA could be observed by the pediatrician.

4. Follow-up 42 months after the first medical history taking: The child was still healthy without symptoms of PFAPA.

Case 4

At the first anamnesis in May 2018, the boy was 15 months old. For seven months, since he was three months old, the boy suffered from recurrent fever attacks of up to 40°C every four weeks for three days. The patient was therefore treated with antibiotics and antipyretics at the local hospital at the age of seven months. At the age of 9 and 12 months, he was treated twice in the St.

Anna Hospital, Vienna, Austria; during the first stay he received cortisone. Examinations at the hospital led to the diagnosis of PFAPA. For the past five months, since the age of ten months, the intervals between three-day fever attacks had shortened, now occurring every two weeks. This change was connected in time to the administration of cortisone. The temperature was highest in the evening up to 40°C. Bronchitis and runny nose were conspicuous in the last attack. The relapses were accompanied by pharyngitis and reddened ears. Aphthae appeared two to three days before the fever attack. Initially, the child responded well to cortisone (Aprednisolon®, Takeda Austria GmbH, Linz, Austria), but no effect was seen in the last attacks. Furthermore, he exhibited swollen cervical lymph nodes. The boy barely sweated during the episodes, his extremities were either warm or cold, and he lay apathetic and stared at the ceiling. The father had suffered from enlarged axillary lymph nodes for years, and the biopsy revealed inflammatory changes. The boy liked to eat eggs; currently he had a green-coloured stool. He slept restlessly and turned around a lot during sleep. He was particularly cuddly before and during the fever. Otherwise, he was a bright child, he was usually soft in character, but could also be stubborn.

Due to the increased fever in the evening as well as the periodicity of 14 days and the soft temperament, the boy received Pulsatilla pratensis LM6, five globules per day for three weeks after the first anamnesis in September 2018. The next flare-up exactly one week later lasted only two days with a maximum temperature of 39.5°C. The flare-up after a further three weeks lasted only one day; the recurrence of fever led to the prescription of five globules of Atropa belladonna CH200 once at the begin of fever.

1. Follow-up 2 months after the first medical history taking: He had no episode since then; aphthous ulcers appeared twice, which previously always heralded a fever episode.

Because of the special preference for eggs and the abdominal distension, the child was given five globules Calcium carbonicum CH200 to strengthen his constitution.

2. Follow-up after five months: after four months, a one-day episode of fever occurred, after a further two weeks a three-day flare-up with temperatures of up to 40°C. The child had canker sores, pharyngitis, reddened tonsils and headache.

During the three-day flare-up he received Atropa belladonna CH200 twice a day for three days and exhibited normal body temperature.

3. Follow-up eleven months after the first medical history taking: The child had a fever for five days, but several children in the kindergarten experienced fever for several days at the same time. Since this time bronchitis was evident without aphthae and pharyngitis, he received Ipecacuanha CH12, two times five

globules per day. The parents said that this was not a PFAPA attack.

4. Follow-up 34 months after the first medical history taking: With the exception of a one-day fever that occurred at the same time as his sister's, the patient has now been well for almost three years. He is in a good mood; the pediatrician could not find any signs of PFAPA anymore.

5. Follow-up 57 months after the first medical history taking: No fever attacks had occurred in the meantime.

Case 5

First history at three years and seven months in October 2020: the girl had experienced difficulties in breathing since early childhood. When she was nine months old, she was diagnosed with human respiratory syncytial virus (RSV). At that time, she was receiving cortisone and bronchodilators. Infectious asthma later developed, which appeared after midnight with dyspnea, dry cough and vomiting. Since the age of two and a half years, a sudden increase in temperature to 40.5°C occurred every four weeks, which lasted for two to five days. The cervical lymph nodes were swollen on both sides. Aphthae and sore throat did not occur. The CRP rose to values of about 200 mg/L. The patient was weak, not aggressive, during and after the fever attacks.

The pediatrician's diagnosis was PFAPA and a tonsillectomy was recommended. Mother's history included monthly angina tonsillar with fever and sore throat when she was 8-9 years old. In retrospect, a PFAPA syndrome could therefore be suspected in the mother. The father had a tonsillectomy as an adult, as had the girl's brother, who also had trouble sleeping due to dyspnea. Because of the periodic and sudden onset of fever and the swollen cervical lymph nodes, Atropa belladonna CH200, five globules, was prescribed once a week.

1. Follow-up two and a half months after the first medical history taking: Two weeks after the beginning of administration of Atropa belladonna CH200, fever had occurred on two days with one day without fever in between. Two months after beginning Atropa belladonna CH200, both the parents and both children were diagnosed with SARS-CoV-2. While the parents were badly affected (the mother experienced fever of up to 38.5°C as well as joint pains and symptoms of a cold; the father suffered from a loss of taste and smell), the children were doing relatively well. The girl was fine again after COVID-19, she just had mild cold symptoms with a runny nose, a slight fever disappeared after a single dose of Atropa belladonna CH200.

Because of the symptoms of a common cold with fever, hoarseness and cough, aching in bones of extremities, she was now given Eupatorium perfoliatum CH12 in a dose of five globules per day for a week, two months and two weeks after first anamnesis.

2. Follow-up three months after the first medical history taking:

The girl was free from fever until a month ago; then she developed fever late in the evening.

Due to her constitution, her preference for ice cream as well as her noticeable empathy in early childhood, she now was given Phosphorus CH12, five globules per day for two weeks. This time the mother noticed that the lymph nodes on the left side of the neck were swollen. The patient also had canker sores in her mouth and her tongue was white. She had slight fever of up to 38.7°C for a total of three days. This reaction was considered to be the first reaction to the HMP by the homeopath.

This was followed by Natrium sulphuricum CH12 to strengthen her constitution because of the child's nocturnal asthma in the anamnesis. Natrium sulphuricum CH12 was given at a dose of five globules per day for three weeks.

3. Follow-up five months after the first medical history taking: There had been no further fever attacks since the last interview. A wound on the leg that has been caused by scratching warts has now healed, the pediatrician had given an antibiotic because the girl had a lot of complaints from the wound and not all HMPs had been available. The mother treated the warts (*Molluscae contagiosae*) with Thuja CH12 for ten days. Not all warts went away, but there was a distinct improvement. The parents were amazed at how well she is doing in general! She had grown a lot in the last few months; it was a real pleasure to see.

4. Follow-up 11 months after the first medical history taking: She was in a good mood; the pediatrician could not find any more signs of PFAPA, nocturnal asthmatic breathing had also improved.

5. Follow-up 34 months after the first medical history taking: No fever attacks had happened since last follow-up.

Case 6

First history at three and a half years in October 2020: The girl had been ill with laryngeal infections, pseudocroup, otitis and angina since she was 8 months old. At an age of 10 months, she had a fever of up to 41°C for the first time lasting for three days; the pediatrician could not determine a focus. The CRP was 160 mg/L. Antibiotics and antipyretics only helped after three days. Following this, the fever attacks initially occurred with a periodicity of seven weeks and duration of four days; after two years with a periodicity of five weeks and duration of five days. All fever attacks were accompanied by aphthae, angina tonsillar, and swollen cervical lymph nodes, but without pharyngitis. She was in a good mood with fever up to 39°C, from 39.5°C she had to lay down. At the age of two years and 8 months, the diagnosis of PFAPA was made in the St. Anna Hospital, Vienna, Austria. At an age of two years and 10 months, bilateral tympanic effusions were diagnosed, and four months later adenoidectomy was performed under general anesthesia.

Because of the recurrent otitis, the adenoids and heavy sweating as well as a preference for eggs, the patient received Calcium carbonicum CH200, and five globules once.

1. Follow-up seven weeks after the first medical history taking: Four days ago a fever attack began with temperatures of up to 41°C, which with a duration of only three days was shorter than ever before, and the interval from the last attack was longer than 8 weeks. The lymph nodes were very swollen, the throat reddened, but no aphthous ulcers appeared at this time.

During the next attack, the girl was given Atropa belladonna CH200. After the attack, Atropa belladonna CH200 was given again, at a dose of five globules once a week for five weeks. One week after the last dose of Atropa belladonna CH200, she received Mercurius solubilis LM12, five globules per day for four weeks. This HMP was chosen because of difficulties during teething, as well as otitis and aggressive behaviour during fever. Aggressive behaviour was not noticed in the following fever attacks.

2. Follow-up four months after the first medical history taking: Another fever attack occurred four weeks ago, and the period between the last two attacks was seven weeks. She was feverish for a week with temperatures of up to 41°C. This was accompanied by swollen lymph nodes, vomiting and stomachache. Strikingly, a punctual rash on the abdomen and back had appeared ten days before the outbreak of both fever attacks. This rash was very itchy; the girl scratched herself to the point of bleeding. Interestingly, this rash had also appeared before the first bouts of fever. The return of old symptoms (skin rash, longer duration of the fever attack) can be interpreted in terms of Hering's rule,¹⁴ which describes that cure takes place in the reverse order of the appearance of symptoms: The symptom that appeared first will be the last one to disappear [14]. The recurrence of old symptoms after administering a HMP is a good sign, especially if at the same time an improvement of the patient's overall condition happens.

Due to the skin symptoms, she now received Sulfur LM6, five globules per day for three weeks.

3. Follow-up seven months after the first medical history taking: The mother was very content since the girl experienced only moderate elevations of temperature up to 38.5°C twice, one day each time. No HMP was prescribed, skin symptoms had disappeared.

4. Follow-up 10 months after the first medical history taking: The girl experienced elevations of temperature for a single day reacting quickly to a dose of Atropa belladonna CH200, but no longer lasting fever attacks. After 8 months, otitis media started on the right side and then extended to the left side. Mercurius solubilis LM 12 controlled the inflammation within three days. The girl was even tempered and showed no signs of PFAPA anymore.

5. Follow-ups 13 and 33 months after the first medical history

taking: No more fever attacks were reported.

Case 7

First history at four and a half years in December 2020: The girl was diagnosed with postpartum muscle hypotonia, so she received physical therapy. Motor development was somewhat delayed. Eight months ago, the patient developed a four-day fever up to 40°C with angina and coated tonsils, aphthae and bilateral swollen cervical lymph nodes for the first time. The symptoms occurred three times with an interval of three weeks, and twice she was given antibiotics. The antibiotics did not help, no evidence of an infectious agent could be found. Antipyretics like Nureflex and Mexalen could only lower the fever for two to three hours each. During the third attack, she received 37.5 mg of cortisone (Aprednisolon®, Takeda Austria GmbH, Linz, Austria). After two hours the fever of 40°C was in the normal range and the effect lasted for 2 days. The episodes recurred every three weeks with four-day bouts of fever thereafter, except six months before first anamnesis when varicella appeared. After varicella, the next bout of fever occurred after six weeks. Three months before first anamnesis, a total resection of the adenoids combined with subtotal resection of the palatine tonsils was performed interrupting periodic fever attacks. One and a half weeks before the first presentation, the patient suffered from a sudden fever again which had been preceded by a fall in kindergarten. With this attack, plaque appeared again on the remains of the tonsil. Since the child often complained of nausea, the pediatrician suggested a follow-up examination in the hospital, where the diagnosis of PFAPA was made.

As the first HMP, Calcium carbonicum CH200 was administered 1 x five globules per week for six weeks. The symptoms leading to this HMP were anxiety in new, unfamiliar situations, sweat on forehead when going to sleep, and a protruding stomach in the otherwise slim girl.

1. Follow-up three months after the first medical history taking: Surprisingly, there were no more attacks of fever, as well as no aphthae, plaque on the residual tonsils or lymph node swellings. Only once did her parents notice short-term fatigue and a low mood. The pediatrician was satisfied regarding muscular hypotonia. A few times there was epistaxis always from the right nostril; once epistaxis lasted for 20 minutes.

Because of the epistaxis and the noticeably pronounced empathy, as well as the preference for ice cream, she was prescribed Phosphorus CH200, five globules per week for six weeks.

2. Follow-up three and a half months after the first medical history taking: Ten days after the last follow-up, there was a strong cough without fever, the pediatrician diagnosed laryngitis. Two days later she developed a fever with vomiting, and during the next day the fever disappeared again. No bacteria were isolated from the throat swab. No medication was administered on the assumption

that it might be a reaction to Phosphorus CH200, especially in combination with the laryngitis. No more epistaxis had occurred since the administration of Phosphorus CH200.

3. Follow-up five months after the first medical history taking: After first prescription no attacks of fever had occurred.

4. Follow-up seven months after the first medical history taking: For three days the girl experienced laryngitis with barking cough and redness of the pharynx. Since the morning, the child had an elevated temperature of 38.0°C with enlarged cervical lymph nodes and one aphthae. The child was given five globules of Atropa belladonna CH200.

5. Follow-up 10 months after the first medical history taking: The fever disappeared within one day. No more fevers occurred since then. The child appeared to be happy without any more signs of PFAPA.

6. Follow-up 32 months after the first medical history taking: The girl was completely healthy with no fever episodes.

Case 8

First history at four years and three months in July 2020: The boy had repeatedly inflamed tonsils: large, red, covered. In addition to the pain caused by tonsillitis, there were also swollen cervical lymph nodes on both sides. He could not eat for two days because of aphthous ulcers. All of this occurred as part of a five-day fever with temperatures above 40°C. The child's history showed febrile seizures in the second year of life for which he was given antibiotics several times (Zithromax®, Azithromycin, Pfizer, Vienna; Tricef®, Cefixim, Merck, Vienna; both Austria). The boy also suffered from laryngitis when he had febrile convulsions for the first time. Two years ago, he came to the hospital because of another attack of fever accompanied by a pronounced rash. At the hospital, the diagnosis of PFAPA was confirmed. An EEG was performed one month later, with normal results. Three months later, bilateral angina was noticed, which was treated with antibiotics. For one and a half year the fever attacks appeared periodically every two months, after treatment with Broncho-Vaxom® (Vifor Pharma, Vienna, Austria) there was a four-month fever-free period. Before the fever, the boy smelled "strange" from the mouth. The fever could reach maximum values of 41°C, antipyretics were of little help. The boy suffered from aphthae, hands and feet were icy cold, red cheeks were noticeable. Physical examination revealed dark circles under the eyes and a rash below the lips. Small vesicles appeared on the right thumb.

The periodicity of 60 days led to the HMP Valeriana officinalis, which the child received in a potency of CH12, five globules per day for four weeks. After that he was given Atropa belladonna CH200, five globules per week for four weeks because of the sudden fever and the ice-cold hands and feet with fever.

1. Follow-up two months after the first medical history taking: There had been no fever attacks, sometimes the patient would say "Everything hurts me!", which he also said earlier during fever attacks. He also reported pain in the mouth, as if aphthous ulcers were coming, but they did not appear. He was now more awake in the evening; his mother fell asleep before him. He had a runny nose, his nose ran with transparent, whitish secretions, and he had a dry cough. At this point the mother told me that her child had been bitten in the face by another boy in the old kindergarten. That hit him very hard, and this incident stayed an issue for him even after more than a year.

Because of the grief and mortification after the bite attack and the transparent secretion from the nose, the homeopath decided on Natrium muriaticum LM6, five globules per day for four weeks.

2. Follow-up four months after the first medical history taking: The patient had a slight runny nose for one day and was now receiving Nux vomica LM6. The mother reported that he had been vaccinated against influenza two days earlier. He still had no fever attacks, only 38°C for one day since the first medical history in July 2020. Now two circular eruptions appeared in the area of the left groin, which developed into crusts and also itched. The mother gave Apis mellifica CH12 because of the itching and Mercurius solubilis LM12 because of the crusts on her own initiative. Interestingly enough, he then occasionally spoke of the boy who had bitten him; maybe because he was supposed to return to the old kindergarten.

Constipation was noticeable in the meantime, which is why he was given Alumina CH12, five globules per day for three weeks.

3. Follow-up six months after the first medical history taking: the constipation had subsided, and there were no further fever attacks. Ear and sore throat pain had occurred three weeks ago, as well as fever for one day. The mother had similar symptoms.

Because of the ear pain emphasized on the right, Mercurius solubilis LM6, two times five globules was prescribed over a day. For two days after that, his eyes were sticky yellow, with Pulsatilla pratensis LM6 these symptoms got better soon. The boy loved to eat tomatoes. Curiously, he requested a HMP that contained tomato. So, Lycopersicum esculentum CH12 was prescribed to him. Another indication was the tendency to severe flu-like infections.

4. Follow-up 8 months after the first medical history taking: The mother reported that after the flu vaccination five months ago the boy developed one day moderate increase of temperature once per month, last time three weeks before. Influenzinum CH200 was prescribed as a single dose of five globules.

The boy reported nightmares; he was an "actor" and had circles under his eyes. He was therefore given five globules of Phosphorus CH200. Overall, his condition was very satisfactory, since there had not been any longer lasting fever attacks since the beginning of

the homeopathic treatment; the current individual fever days were uncomplicated and only with mild elevations in body temperature.

5. Follow-up 12 months after the first medical history taking: No fever attacks had happened - only minor skin rashes appeared. His behaviour was sometimes strange: When having failed to do something correctly, he hit his forehead. He told his mother: "You will die soon! Because you are so old!"

6. Follow-up 15 months after the first medical history taking: Three days before follow-up, fever occurred for two days accompanied by pharyngeal pain. After a single dose of Atropa belladonna CH200 the fever disappeared after 24 hours. He was otherwise happy and has no symptoms of PFAPA anymore. The mother was very satisfied with the good condition of her child.

7. Follow-up 36 months after the first medical history taking: There were no more flares during the last 14 months.

Case 9

Since the age of two, the 32-month-old boy had attacks of fever for two to four days every two to four weeks. The pediatrician diagnosed PFAPA. During the first four attacks, the mother noticed bad odor from his mouth. He cried, but was not aggressive with a fever. He had a preference for ice cream and cold milk. Considering the symptoms of reddening of the tonsils, swelling of the cervical lymph nodes, a watery runny nose, and snake-like movement of the tongue, the HMP Mercurius solubilis LM6, five globules per day for four weeks was chosen. The parents were advised that in case of fever, Atropa belladonna CH200 should be given. Three weeks after the initial medical history taking in May 2020, another episode occurred, and Atropa belladonna CH200 was given. The fever lasted only one and a half day.

1. Follow-up six months after the first medical history taking: The last period of fever had been three and a half weeks ago. The temperature was 39°C only for one day; otherwise the temperature was significantly lower for three days. Because of his stubborn character, he was now given Lycopodium clavatum CH30.

2. Follow-up 10 months after the first medical history taking: The boy had repeated attacks of fever that lasted up to three days, but were less severe than in the time before the homeopathic treatment. The situation was not yet satisfactory.

3. Follow-up 14 months after the first medical history taking: The boy experienced a five days fever period. He was very cuddly and lovely with very little hunger, but drank quite well as usual and a lot, preferably cold. The tonsils were reddened. He would like to sleep and to be covered up, his body was warm everywhere. While sleeping he whimpered slightly.

It was decided to prescribe Arsenicum album CH200. Since the situation did not change, he received Atropa belladonna CH200

the next day. While fever continued, a red eruption arose on his left cheek. Therefore, Lachesis muta CH200 was given. Lachesis muta CH200 was repeated; the fever disappeared after 5 days.

4. Follow-up 16 months after the first medical history taking: He was suffering from dry cough. He received five globules of Lycopodium clavatum CH30, the cough disappeared within two days.

5. Follow-up 32 months after the first medical history taking: He still experienced irregular flares of fever, however, lasting only one or two days. This case was classified as unsuccessful.

Case 10

The girl was three and a half years old at the first anamnesis in September 2020. One and a half years ago she had her first fever; for a year now, a record had been kept of the fever, which occurred every three and a half weeks and lasted for four to five days. The fever reached values of 40°C during that time. The fever was accompanied by nausea, which led to the refusal of solid food. There were also swollen cervical lymph nodes on the right side, a bright red face, one to two aphthous ulcers, sore throat, and tearing off her neck scarf. After the attack, the gums were swollen and bleeding.

PFAPA syndrome was diagnosed at the children's hospital. Because of the sudden fever and the bright red face with cold hands and feet, the patient received Atropa belladonna CH200, five globules per week for four weeks.

1. Follow-up six weeks after the first medical history taking: After five weeks there was a fever for four days, a temperature of 39.7°C was measured only once, otherwise the values were far lower. The lymph nodes were also far less swollen. She also walked around as if she were not ill. Atropa belladonna CH200 was repeated.

2. Follow-up two months after the first medical history taking: the girl was fine, though tantrums were noticed again, as she had in the past. In kindergarten, she was shy and preferred to watch the other children. She now received Pulsatilla pratensis CH12 five globules per day for 10 days.

3. Follow-up 7 months after the first medical history taking: She was doing well; the last attack was more than two months ago. Before, there were never two months without an attack. She was still easily angered and extremely stubborn until she got what she wanted. Her father was currently not allowed to put her to bed. She was a little less shy in kindergarten. She now received Lycopodium clavatum CH200, five globules per week, until anger was relieved.

4. Follow-ups 13 months and 35 months after the first medical history taking: There had been neither any attacks of fever nor any other signs of PFAPA.

Discussion

Although PFAPA syndrome is a polygenic or multifactorial disease with an unidentified genetic background, it is the most frequent auto-inflammatory condition in childhood and must frequently be considered part of the differential diagnosis of some monogenic disorders in children and adults [15]. Although this disease has a favourable course and generally, resolves as the child grows older, it can have a significant impact on the quality of life of the child and his or her caregivers [5]. The disease usually begins before the age of 5, and PFAPA usually regresses by puberty [16]. In the here reported cases, we find an age of about 4 years, when PFAPA was resolved. Current conventional therapy of PFAPA includes cortisone and colchicine. Glucocorticoids are suggested as the treatment of choice in PFAPA syndrome, because their prompt administration is able to terminate the attacks rapidly and completely in the majority of patients. Such strong response is usually considered a peculiar diagnostic feature in pediatric and adult patients [17]. The conventional dosage from 0.5 to 2 mg/kg of prednisone (or equivalent) in a single dose at the time of fever onset has been proved useful in a randomized clinical trial, and therefore, glucocorticoids can be recommended in PFAPA patients with a level of evidence 2B [18]. While caretakers of the children confirmed immediate response to cortisone, they also observed relapses and subsequently shorter time intervals between the PFAPA flares. Furthermore, many caretakers were reluctant to administer cortisone to their children due to possible adverse effects or possible negative effects regarding hormone imbalance. In 303 PFAPA patients from a tertiary Turkish Center, colchicine was used as regular prophylactic treatment with high rate of response in terms of reduction of the frequency of episodes [19]. Interestingly, heterozygous mutations in the familial Mediterranean fever virus (MEFV) gene were found in 25% of PFAPA subjects, who obtained even better results in terms of reduction of attacks. The potential modifier role of MEFV mutations in PFAPA patients seems associated with attenuated disease severity and higher response rate to colchicine compared to non-carriers of MEFV variants [18].

Antipyretics may be effective therapy for some children and are a reasonable option, especially for caretakers who are reluctant to use daily medication and are concerned about steroid side effects, or are concerned about the risks and potential consequences of tonsillectomy [20]. However, the caretakers of the children observed that antipyretics only brought about a very short fever reduction, if any, and that the children tended to have a longer duration of fever rather than a shorter one.

Of note, the evidence for the effectiveness of tonsillectomy in children with PFAPA syndrome is based on a systematic review that included two small randomized controlled trials studying the effects of tonsillectomy compared to no surgery. Tonsillectomy was associated with immediate and complete clinical resolution and

significant reduction in the frequency and severity of symptoms. Although these results have to be interpreted considering the clinical severity, the previous response to a single dose of prednisone, and the surgical risk in every individual situation, tonsillectomy as a therapy for PFAPA syndrome can be recommended with a level of evidence 1A [21].

There is considerable heterogeneity in management strategies and a lack of evidence-based treatment guidelines. Consensus treatment plans (CTPs) are standardized treatment regimens that are derived based upon best available evidence and current treatment practices. CTPs are a way to enable comparative effectiveness studies to identify optimal therapy, and are less costly to execute than randomized, double blind placebo controlled trials [20]. The purpose of the described project was to develop CTPs and response criteria for PFAPA. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) PFAPA Work Group is composed of pediatric rheumatologists, infectious disease specialists, allergists/immunologists and otolaryngologists. An extensive literature review was conducted followed by a survey to assess physician practice patterns. This was followed by virtual and in-person meetings between 2014 and 2018. Nominal group technique was employed to develop CTPs, as well as inclusion criteria for entry into future treatment studies, and response criteria. Consensus required 80% agreement. The PFAPA working group developed CTPs resulting in 4 different treatment arms: 1. Antipyretic, 2. Abortive (corticosteroids), 3. Prophylaxis (colchicine or cimetidine) and 4. Surgical (tonsillectomy). Consensus was obtained among CARRA members for those defining patient characteristics who qualify for participation in the CTP PFAPA study. The goal is for the CTPs developed by this group to lead to future comparative effectiveness studies that will generate evidence-driven therapeutic guidelines for this periodic inflammatory disease [20]. It might be of interest to increase the present treatment arms by an homeopathic arm since the results of here presented case series indicate that 9 out of 10 children (90 %) have shown a strong time-dependent improvement to homeopathic therapy. Furthermore, several parents spontaneously reported that their children had made a leap in development at the same time as their health improved [20].

The advantage of homeopathy is that it is inexpensive, resilience/health promoting and there are no adverse effects when properly applied. Furthermore, there are no interactions with conventional therapies and no stress on the metabolism of the children. A disadvantage is the insufficient number of experienced homeopathic doctors at this time.

Conclusion

Since the children in our study suffering from PFAPA have responded so favourably and showed an early resolving of the disease in infancy, individualized homeopathic treatment could be

considered as another very effective option for the treatment of PFAPA. Further studies are needed to substantiate the effectiveness of homeopathy in PFAPA.

Declarations

Ethics Approval: All the studies were conducted in accordance with the Declaration of Helsinki. The study was approved by the Ethical Committee of the Sigmund Freud Private University, Vienna, Austria (Ethics Committee Application No. 803-2023) as of July 6, 2023; ClinicalTrials.gov Identifier: NCT05995288. Informed consent and assent were obtained from the parents, before commencing retrospective study procedures. Consent for publication: Written informed consent was obtained from the parents of the patient for publication of these case reports.

Competing interests: Authors declare that there are no competing interests.

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Authors' contributions: Jorgos Kavouras: Conceptualization, Methodology, Software, Writing—original draft, Writing—review & editing, Project administration. Michael Frass: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing, Supervision. Kavita Chandak: Methodology, Writing – review & editing, Supervision. Juergen Ivanis: Validation, Writing – original draft, Supervision. Tadeusz Peter Panhofer: Investigation, Writing – original draft. Petra Weiermayer: Conceptualization, Writing – original draft, Writing – review & editing, Supervision.

Conflict of Interest Disclosures (includes financial disclosures): None of the authors has conflicts of interest to disclose.

Clinical Trial Registration: ClinicalTrials.gov Identifier: NCT05995288, <https://clinicaltrials.gov/>; individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures and appendices) will be shared.

Article Summary: Homeopathy showed a time-dependent improvement in PFAPA in terms of frequency of relapses, intensity of symptoms to complete disappearance of the disease.

What's Known on This Subject: Periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome is frequently diagnosed in young children. Fevers recurring at a nearly predictable rate every three to eight weeks are the signature symptom of PFAPA syndrome possibly lasting until adolescence.

What This Study Adds: Individualized homeopathy works well in patients with PFAPA. There was a time-dependent improvement with regard to frequency of flares, intensity of symptoms, up to complete disappearance of disease.

Contributors Statement: Prof. Jorgos Kavouras substantially conceptualized and designed the study, supervised data collection, drafted the initial manuscript, and critically reviewed and revised the manuscript. Dr. Kavita Chandak, Juergen Ivanis, Prof. Tadeusz Peter Panhofer and Dr. Petra Weiermayer substantially contributed to conception and design of the study, analyzed and interpreted data, and critically reviewed and revised the manuscript. Prof. Michael Frass substantially conceptualized and designed the study, designed the data collection instruments, collected data, carried out the initial analyses, treated the patients, drafted the initial manuscript, and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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