Case Report

Intrafamilial Variable Phenotypic Expression of a *CIAS1* Mutation: From Muckle-Wells to Chronic Infantile Neurological Cutaneous and Articular Syndrome

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ABSTRACT. Among hereditary inflammatory disorders, Muckle-Wells syndrome, chronic infantile neurological cutaneous and articular syndrome (CINCA), and familial cold urticaria have recently been shown to be caused by dominantly inherited mutations in the *CIAS1* gene. Reports suggest that these 3 diseases result from distinct missense mutations, with very few overlapping symptoms. We describe a French family presenting an intrafamilial overlapping clinical phenotype of CINCA and Muckle-Wells syndrome, caused by a mutation in *CIAS1* gene. Clinical and genetic observations suggest that Muckle-Wells syndrome, CINCA, and familial cold urticaria are various phenotypic expressions of the same disease. (J Rheumatol 2005;32:747–51)

Key Indexing Terms:
HEREDITARY FEVER SYNDROMES
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Hereditary periodic fever syndromes are defined by recurrent attacks of generalized inflammation for which no infectious or autoimmune cause can be identified. Among these hereditary systemic inflammatory diseases, Muckle-Wells syndrome (MWS) is characterized by acute febrile inflammatory episodes of arthritis and urticaria[1-5]. Subsequent progressive nerve deafness develops and after several years of evolution, the disease may be complicated by multiorgan AA-type amyloidosis with renal involvement leading to endstage renal failure. Familial cold autoinflammatory syndrome (FCAS), also known as familial cold urticaria, is characterized by intermittent rash, arthralgia, fever, and conjunctivitis after generalized cold exposure[6-10], whereas chronic infantile neurological cutaneous and articular syndrome (CINCA) is characterized by the triad of chronic cutaneous urticaria, chronic meningitis, and arthropathy. CINCA starts most often at birth and persists for the whole lifespan of the patient. Common morphological features characterize these patients with typical facial dysmorphia, short stature, and clubbing fingers[11-14]. Table 1 summarizes the clinical manifestations of these diseases.

Mutations of *CIAS1* gene encoding the protein cryopyrin have recently been shown to underlie the 3 diseases[15-19]. The first findings suggested that the different phenotypes resulted from distinct missense mutations, with very few overlapping symptoms[17]. More recent data increase the total number of known germline mutations in *CIAS1* to 36, indicating that a single *CIAS1* mutation may cause 2 or even the 3 syndromes[20-22]. Nevertheless, to our knowledge different members of the same family present the same phenotypic expression.

We describe a French family presenting an overlapping clinical phenotype of CINCA and MWS caused by a mutation in *CIAS1* gene (A439V), previously described as FCAS[19].

CASE REPORTS

An 8-year-old boy (Patient III-3, Figure 1) was referred to our pediatric unit for chronic urticaria, arthralgia, and growth retardation. Permanent nonpruritic urticarial eruption, for which no precipitating factor could be found, had been present since birth. From 6 months of age, he had also had recur-

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Table 1. Clinical features of MWS, FCAS, and CINCA.

	MWS	FCAS	CINCA
Age of onset	First or second decade	Before age 6 mo	At birth
Morphological features	Not specific	Not specific	Frontal bossing, saddle-nose, micrognathia, clubbing fingers, growth delay
Precipitating factor	Various (stress, infections, etc.)	Cold exposure	Not known
Fever	During acute episode	Within a few hours of cold exposure	During flares
Dermatologic features	Recurrent urticaria during acute episodes	Itchy or burning urticaria during acute episodes	Nonpruritic chronic urticaria
Joint symptoms	Arthralgia, not destructive polyarthritis	Polyarthralgia, without arthritis	Mild to severe symmetric polyarthritis with radiological modifications
Sensory organ involvement			
Eye	No	Conjunctivitis	Ocular inflammation with optic atrophy
Ear	Progressive nerve deafness	No	Progressive nerve deafness
Neurological involvement	No	No	Chronic meningitis, cerebral atrophy, dura calcifications
Additional common symptoms	Abdominal pain	Sweating, drowsiness, headache, thirst, nausea	Hepatosplenomegaly, adenomegaly
Duration of acute episode	2–3 days, sometimes up to 1 week	Less than 24 hours	Variable (up to weeks)
Secondary amyloidosis	Common (10–50%)	Rare (2%)	Rare

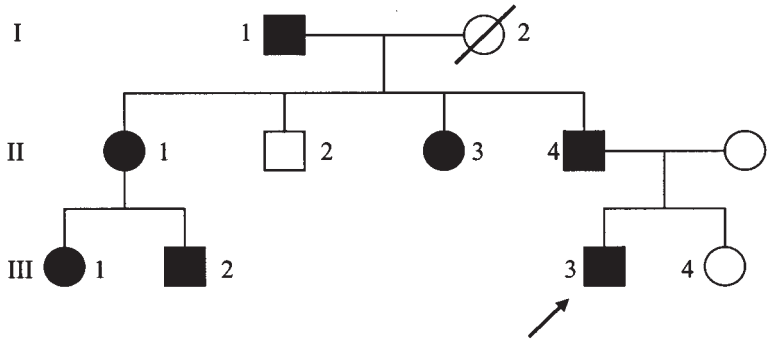

Figure 1. Pedigree of a French family with hereditary autoinflammatory disorder.

rent fever attacks, associated with arthritis and aphthous mouth ulcers. Clinical and biological examinations excluded an infectious cause of these recurrent symptoms. He failed to thrive correctly and at the age of 8 his height and weight were at –2.5 standard deviations.

Examination revealed a facial dysmorphia with frontal bossing, a saddle-nose, and slight micrognathia (Figure 2). Urticaria was present at every examination, with some flares during fever attacks. Clinical features during a fever attack comprised large polycyclic mouth ulcers, ulcerative keratitis, splenomegaly, adenomegaly, and severe oligoarthritis, mostly of the knees, ankles, and elbows. Besides the ulcerative keratitis, ocular examination revealed myopia and episcleritis, but no other manifestation such as optical disk edema or anterior uveitis. Arthritis always resolved spontaneously, without radiological modifications, within one or 2 weeks. Neurological involvement was not observed: a lumbar puncture during a fever attack at the age of 8 years revealed a strictly normal cerebral spine fluid composition, and tomodensitometry of the brain showed no abnormalities such as cerebral atrophy or dura calcifications. The audiogram revealed no hearing loss.

Laboratory examinations revealed moderate features of inflammation during fever attacks. Interestingly, during a fever attack at the age of 8, polymerase chain reaction (PCR) for human herpes virus 6 (HHV6) was positive in blood, saliva, and lumbar fluid. Subsequently, viral culture of blood and saliva confirmed circulating HHV6 during the inflammatory flares, with disappearance of circulating HHV6 during the remissions of fever.

Family history revealed roughly similar symptoms in the father, grandfather, 2 aunts, and 2 cousins of the proband (Figure 1, Table 2). The father (subject II-4) had a less severe clinical presentation. He mainly has chronic urticaria accompanied rarely by fever (average once a year). Since the age of 10 years he has had recurrent headache, responding well to paracetamol. He had not had clinical investigations such as brain tomodensitometry or lumbar puncture. Articular, ocular, and neurosensory involvement was not observed in the father.

Clinical manifestations of one aunt (subject II-1) started at the age of 12 years with nonerosive arthritis of the ankles and recurrent conjunctivitis. No precipitating factor could be found for the recurrent nonerosive arthritis. Since the age of 21 years, she had had intermittent episodes of rash, occurring after prolonged orthostatism or generalized exposure to cold. Microscopic examination of a lesional skin biopsy showed a superficial perivascular and interstitial infiltrate of lymphocytes and polymorphonuclear cells and mild non-necrotic leukocytoclastic vasculitis. Further, she had chronic anterior uveitis, but no other neurosensory involvement. Laboratory studies showed only slight inflammatory signs during fever attacks, without autoimmune markers.

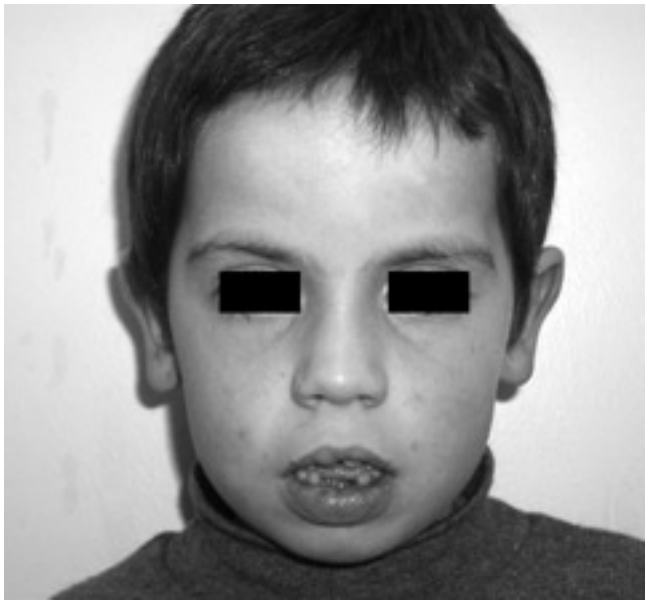

Figure 2. Morphologic features of patient III-3. Note the frontal bossing, micrognathia, saddlenose deformity, and mouth ulcers.

The other aunt (II-3) differs from the other members of the family, with severe, permanent, nonerosive arthritis of the knees and ankles, which had begun at the age of 13 and responded well to local steroid injections. Cutaneous manifestations included acrocyanosis, permanent livedo of legs and wrists, and since the age of 19, recurrent erythematous macules and patches. Ocular manifestations (mainly acute anterior uveitis and recurrent ulcerative keratoconjunctivitis) led to a progressive severe visual acuity loss in both eyes. Like the other members of this family, subject II-3 has recurrent fever with inflammatory signs during flares. Autoimmune laboratory markers were all negative. To control arthritis, she received medications such as hydroxychloroquine sulfate or general steroid therapy, with no decrease of symptoms.

The other affected members of the family (subjects I-1, III-1, and III-2) have mainly ocular (ulcerative keratitis), cutaneous (chronic urticaria), and articular (recurrent nondestructive arthritis) manifestations. Only the proband displays specific morphologic features comprising frontal bossing, saddle-nose, micrognathia, and growth retardation. No evidence of secondary amyloidosis or hearing loss was found in any member of this family.

Mutation investigations. Peripheral blood was obtained from patients, and DNA was extracted as described[16]. A mutation search was performed from genomic DNA after PCR amplification of the 9 exons of the *CIAS1* gene using oligonucleotides and experimental conditions as described[19]. Briefly, free nucleotides and oligonucleotides were eliminated by exonuclease I, 10 units (USB^{TM}), and shrimp alkaline phosphatase, 1 unit (USB^{TM}), treatment at 37°C for 15 min followed by incubation at 80°C for 15 min. Mutation detection was performed by fluorescent sequencing with dye-terminator chemistry (Perkin Elmer) on a 3100 automated sequencer (ABI Perkin Elmer).

Mutation analysis of the *CIAS1* gene encoding cryopyrin was carried out in subjects II-3, II-4, and our patient by sequencing the coding exons of the gene. A heterozygous variant in exon 3 resulting in an arginine-to-valine substitution at position 439 was identified in the 4 patients tested. The other affected members of the family refused genetic testing.

DISCUSSION

The family described here has clinical features of autosomal dominant systemic inflammatory disease, but the clinical presentation of the affected members did not exactly fit any of the hereditary inflammatory disorders. Indeed, they displayed symptoms from both Muckle-Wells and CINCA syndromes (Table 1)[1-5,11-14]. In the proband, facial dysmorphia, growth retardation, and the splenomegaly during acute episodes could suggest CINCA syndrome, but at age 8 years he did not have the 2 other major criteria of this disease —

Table 2. Summary of clinical features of the different family members.

	Patient I-1	Patient II-1	Patient II-3	Patient II-4	Patient III-1	Patient III-2	Proband, Patient III-3
Age of onset	?	12 yrs	13 yrs	< 5 yrs	< 5 yrs	< 5 yrs	6 mo
Special morphologic features	No	No	No	No	No	No	Yes
Dermatologic features							
Chronic urticaria	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Other	?	—	Acrocyanosis, livedo	—	—	—	Mouth ulcers
Fever	?	Yes	Yes	Yes	No	No	Yes
Precipitating factor	?	Cold exposure	—	—	—	—	—
Joint symptoms	Nondestructive polyarthritis during flares	Nondestructive polyarthritis during flares	Severe permanent nondestructive arthritis	No	Nondestructive polyarthritis during flares	Nondestructive polyarthritis during flares	Nondestructive polyarthritis during flares
Eye involvement	Ulcerative keratitis	Conjunctivitis, uveitis	Keratoconjunctivitis, uveitis	No	Ulcerative keratitis	Ulcerative keratitis	Ulcerative keratitis, uveitis
Hearing loss	No	No	No	No	No	No	No
Neurological involvement	No	No	No	Recurrent headache	No	No	No
Hepatosplenomegaly, adenomegaly	?	No	No	No	No	No	Yes
A439V mutation	Not tested	Yes	Yes	Yes	Not tested	Not tested	Yes

?: not known.

central nervous system involvement and destructive arthropathy. Nevertheless, these major criteria could still develop over time, so further followup of this patient is necessary.

A French patient recently described by Granel, *et al*[23] presented characteristics roughly similar to those of our proband (nonpruritic generalized urticaria with inflammatory flares, joint manifestations, slightly dysmorphic facial appearance, and clubbing of the fingers). However, our patient had no mental retardation, suggesting more likely CINCA syndrome, or hearing loss. Moreover, the family history is not consistent with familial CINCA syndrome. Indeed, in other affected family members, the disease more closely resembles MWS, as they have nondestructive arthritis and urticarial rash only during fever attacks. Only one aunt (subject II-3) has chronic arthritis of the ankles and knees, but radiological findings did not show the typical cartilaginous modifications described in CINCA syndrome. It is notable that the mutation search in *CIAS1* of 4 affected members of the family revealed the A439V mutation, which was previously described in a family with typical FCAS[19]. Only one of our subjects (II-1) had disease symptoms after generalized cold exposure. All these observations suggest that MWS, CINCA, and FCAS could be various phenotypic expressions of the same disease. The clinical presentation of this autoinflammatory disease could still depend on unknown factors such as environmental influences, involvement of modifier genes determining the clinical phenotype, or associated genetic polymorphisms. The latter possibility is reinforced by the fact that some CINCA patients with typical clinical presentation have no mutations in the *CIAS1* gene[20].

Interestingly, the reactivation of the inflammatory manifestations in the 8-year-old patient was accompanied by circulating HHV-6. Infection with HHV-6 is very common and usually not associated with severe human disease. After primary infection (causing exanthem subitum), the virus replicates in the salivary glands and is shed in saliva. It remains latent in lymphocytes and monocytes and persists at low levels in cells and tissues. In the immunosuppressed patient, HHV-6 has been recognized as an opportunistic pathogen[24,25]. Furthermore, it has been incriminated in the pathogenesis of autoimmune diseases: it has reportedly been associated with a wide variety of diseases such as lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis, and juvenile idiopathic arthritis[26-28]. The role of HHV6 as the trigger of fever attacks or as a consequence of them in this family remains to be elucidated.

In summary, clinical symptoms and genetic analysis of our family suggest that FCAS, MWS, and CINCA could be different phenotypic expressions of the same disease due to mutations in the *CIAS1* gene. Further analysis of these inflammatory diseases is necessary to assess factors determining the phenotypic expression of *CIAS1* gene mutations. Laboratory findings from our patient suggest that HHV6 could be one of the modifier factors determining the clinical phenotype of these autoinflammatory diseases.

REFERENCES

1. Muckle TJ, Wells M. Urticaria, deafness, and amyloidosis: a new heredo-familial syndrome. Q J Med 1962;312:35-48.
2. Barriere H, Prost A, Wallex B. Le syndrome de Muckle-Wells. Ann Dermatol Venereol 1977;104:664-6.
3. Muckle TJ. The 'Muckle-Wells' syndrome. Br J Dermatol 1979;100:87-92.
4. Watts RA, Nicholls A, Scott DG. The arthropathy of the Muckle-Wells syndrome. Br J Rheumatol 1994;33:1184-7.
5. Lieberman A, Grossman ME, Silvers DN. Muckle-Wells syndrome: case report and review of cutaneous pathology. J Am Acad Dermatol 1998;39(2 Pt 1):290-1.
6. Kile RL, Rusk HA. A case of cold urticaria with an unusual family history. JAMA 1940;114:1067-8.
7. Doeglas HM. Familial cold urticaria. Arch Dermatol 1973;107:136-7.
8. Commerford PJ, Meyers OL. Arthropathy associated with familial cold urticaria. S Afr Med J 1977;51:105-8.
9. Zip CM, Ross JB, Greaves MW, Scriver CR, Mitchell JJ, Zoar S. Familial cold urticaria. Clin Exp Dermatol 1993;18:338-41.
10. Hoffman HM, Wanderer AA, Broide DH. Familial cold autoinflammatory syndrome: phenotype and genotype of an autosomal dominant periodic fever. J Allerg Clin Immunol 2001;108:615-20.
11. Dollfus H, Hafner R, Hofmann HM, et al. Chronic infantile neurological cutaneous and articular/neonatal onset multisystem inflammatory disease syndrome: ocular manifestations in a recently recognized chronic inflammatory disease of childhood. Arch Ophthalmol 2000;118:1386-92.
12. Guillet G, Dupre D, Guillet MH, et al. Bi-symptomatic CINCA syndrome with inaugural urticaria and major articular lesions. Ann Dermatol Venereol 1999;126:331-4.
13. Prieur AM, Griscelli C, Lampert F, et al. A chronic, infantile, neurological, cutaneous and articular (CINCA) syndrome. A specific entity analysed in 30 patients. Scand J Rheumatol 1987;66 Suppl:57-68.
14. Prieur AM. A recently recognised chronic inflammatory disease of early onset characterised by the triad of rash, central nervous system involvement and arthropathy. Clin Exp Rheumatol 2001;19:103-6.
15. Aksentijevich I. Mutations in CIAS1 establish NOMID/CINCA in the spectrum of genetic disorders in the pyrin/marenostrin family of autoinflammatory diseases. Third International Conference on Familial Mediterranean Fever and Hereditary Inflammatory Disorders. La Grande Motte, France; 2002.
16. Cuisset L, Drenth JP, Berthelot JM, et al. Genetic linkage of the Muckle-Wells syndrome to chromosome 1q44. Am J Hum Genet 1999;65:1054-9.
17. Feldmann J, Prieur AM, Quartier P, et al. Chronic infantile neurological cutaneous and articular syndrome is caused by mutations in CIAS1, a gene highly expressed in polymorphonuclear cells and chondrocytes. Am J Hum Genet 2002;71:198-203.
18. Hoffman HM, Wright FA, Broide DH, Wanderer AA, Kolodner RD. Identification of a locus on chromosome 1q44 for familial cold urticaria. Am J Hum Genet 2000;66:1693-8.
19. Hoffman HM, Mueller JL, Broide DH, Wanderer AA, Kolodner RD. Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome. Nat Genet 2001;29:301-5.
20. Aksentijevich I, Nowak M, Mallah M, et al. De novo CIAS1 mutations, cytokine activation, and evidence for genetic

heterogeneity in patients with neonatal-onset multisystem inflammatory disease (NOMID): a new member of the expanding family of pyrin-associated autoinflammatory diseases. Arthritis Rheum 2002;46:3340-8.
21. Sarrauste de Menthiere C, Terriere S, Pugnere D, Ruiz M, Demaille J, Touitou I. INFEVERS: the Registry for FMF and hereditary inflammatory disorder mutations. Nucleic Acids Res 2003; 31:282-5.
22. Dode C, Le Du N, Cuisset L, et al. New mutations of CIAS1 that are responsible for Muckle-Wells syndrome and familial cold urticaria: a novel mutation underlies both syndromes. Am J Hum Genet 2002;70:1498-506.
23. Granel B, Philip N, Serratrice J, et al. CIAS1 mutation in a patient with overlap between Muckle-Wells and chronic infantile neurological cutaneous and articular syndromes. Dermatology 2003;206:257-9.
24. Campadelli-Fiume G, Mirandola P, Menotti L. Human herpesvirus 6: An emerging pathogen. Emerg Infect Dis 1999;5:353-66.
25. Kosuge H. HHV-6, 7 and their related diseases. J Dermatol Sci 2000;22:205-12.
26. Mizukawa Y, Shiohara T. Virus-induced immune dysregulation as a triggering factor for the development of drug rashes and autoimmune diseases: with emphasis on EB virus, human herpesvirus 6 and hepatitis C virus. J Dermatol Sci 2000;22:169-80.
27. Toyabe S, Harada W, Suzuki H, Hirokawa T, Uchiyama M. Large vessel arteritis associated with human herpesvirus 6 infections. Clin Rheumatol 2002;21:528-32.
28. Wiersbitzky S, Ratzmann GW, Bruns R, Wiersbitzky H. Reactivation in children of juvenile chronic arthritis and chronic iridocyclitis associated with human herpesvirus-6 infection. Padiatr Grenzgeb 1993;31:203-5.