Chilblains as a Diagnostic Sign of Aicardi-Goutières Syndrome

Abstract

Aicardi-Goutières syndrome (AGS) is a genetically heterogeneous disorder showing variability in age of onset and clinical features. Chilblain lesions have been described in AGS patients and recent papers have discussed the clinical, molecular and cutaneous histopathological overlap with chilblain lupus. Here we report on 2 unrelated children with AGS and chilblain lesions, whose clinical histories and examination findings well illustrate the wide phenotypic variability that can be seen in this pleiotropic disorder. Although both patients show remarkable similarity in the histopathology of their associated skin lesions, with thrombi formation, fat necrosis and hyalination of the subcutaneous tissue, we note that the histopathology reported in other AGS cases with chilblains does not necessarily demonstrate this same uniformity. Our findings highlight the significant role of the characteristic chilblain skin lesions in the diagnosis of AGS, and variability in the associated histopathology which may relate to the stage and severity of the disease.
Chilblains typically develop after the first year of life, occurring particularly on the toes, fingers and outer helix of the ears, and show exacerbation with cold weather. Variable severity is well recognized, ranging from otherwise isolated cold hands and feet (in the absence of overt chilblains) to severe tissue damage and autoamputation. Most typically, chilblains appear as a purplered swelling of the digits and ears. The lesions may result from an inflammatory vasculopathy with microvascular injury leading to thrombi formation [13, 14]. In spite of the high frequency of such skin lesions in AGS patients, few reports describing the cutaneous histopathological features of the condition have been published [8, 13, 14].

Herein, we describe 2 patients showing different clinical features and courses, but in both of whom the clinical picture is fully compatible with a diagnosis of AGS. Genetic testing in one child revealed a homozygous mutation in TREAT1 thus confirming the diagnosis of AGS. The other child harbours an intragenic deletion of the AGS gene, SAMHD1. Of note, both children show a remarkable similarity in the histopathological features of their skin lesions. These data highlight the significance of chilblain lesions in the diagnosis of AGS and the importance of histopathological examination in AGS-related skin disease.

Case Reports ▼

Patient 1

This male was the third child born to a 27-year-old mother and 42-year-old father. The parents are maternal and paternal first cousins (double consanguineous). The first and fourth pregnancy resulted in 2 daughters, one died immediately after birth of an undefined cause, the other succumbed 15 days after birth with respiratory distress. A postmortem examination was not performed for either deceased sibling. There was no family history of chilblains or autoimmune disease. TORCH screening (Toxoplasmosis, Rubella, CMV, Herpes simplex), before pregnancy and in the 12th and 34th week of gestation, together with serial ultrasound examination throughout the pregnancy, were normal. The child was born at 42 weeks by spontaneous vaginal delivery after an uncomplicated pregnancy. Neonatal anthropometric parameters were not recorded but mentioned to be normal. There were no neonatal problems. He was breast-fed and gained weight satisfactorily. He was healthy until the age 6 months when the parents noticed increasing size of the left eye and clouding of the cornea. Ophthalmological examination under anaesthesia showed a normal corneal diameter but increased intraocular pressure in the left eye diagnosed as open angle glaucoma. Intraocular pressure was controlled with a topical beta-blocker and carbonic anhydrase inhibitor. At that time, serology for TORCH infections and antibodies to adenovirus and enterovirus were negative.

He was assessed at age 13 months because his parents noticed episodes of fever recurring at a frequency of approximately once a week and lasting 3 days at a time. The fever was not accompanied by encephalopathy, irritability or disturbed sleep pattern. The child was hospitalized for diagnostic investigations (including blood count, urine analysis, CRP, ESR, immunoglobulin levels and complement) all of which were unremarkable. He underwent routine vaccination without complications. At this time, his developmental milestones reflected a mild delay, only fully supporting his head at the age of 9 months, sitting supported at age 12 months, standing with support at 18 months, saying meaningful words at age 17 months, and speaking in sentences at 2½ years.

At the age of 2 years it was noticed that he was unable to stand with support as he had previously. Cerebral computed tomography (CT) performed at this time revealed bilateral tiny calcifications in the basal ganglia (Fig. 1). A subsequent CT performed at the age of 5½ years demonstrated increased density of the observed basal ganglia calcification (Fig. 1).

At the age of 3 years he developed a persistent skin rash involving the hands, feet and helices of the ear. These lesions were significantly exacerbated by cold. There was no history of photosensitivity, weight loss, immune deficiency, or malignancy. In the active period, the affected areas were erythematous and swollen. Some pedal lesions ulcerated to result in destruction of the distal joints of the toes. Healing produced well circumscribed scaly erythematous plaques and areas of atrophic skin (Fig. 1). This process lasted for at least 3 months. Within 3 years his condition progressed to affect the upper limbs and produce necrosis at the toes. In view of the skin manifestations and a high ESR (92 and 125 in first and second hour, respectively), a diagnosis of systemic lupus was considered. However, this diagnosis was subsequently discounted on the basis of normality of antinuclear antibodies (ANA) titres, lupus anticoagulant, and protein C activity. Further, antiphospholipid antibodies, anticardiolipin IgG and IgM, alpha-1 antitrypsin, cryofibrinogen, cryoglobulins, complement levels (C4 and C8), and coagulation indices were also negative.

Biopsy performed at the edge of a necrotic skin lesion showed no hyperkeratosis, and normal epidermis and dermis (Fig. 3). However, there were thick-walled vessels with intra-vascular thrombosis, necrosis of fat cells (marked by a loss of nuclei), and a network of hyaline deposits between the fat cells. Direct immunofluorescence of IgM was negative. We first examined the patient at the age of 5½ years. His weight, length and head circumference were 13.5 kg (−2.5 SD), 89.5 cm (−4 SD) and 50 cm (−15 SD), respectively. We observed a large left cornea, facial erythema, and multiple erythematous purple chilblain lesions of the upper and lower limbs and on the sides of both feet. Areas of necrosis with crust formation were also seen on these plaques. He exhibited uncoordinated, dystonic arm movements. Tone was increased and deep tendon reflexes were hyperactive in the upper and lower limbs. Ophthalmoscopy showed tigroid fundi with relatively poor pigmentation of the macula and a small macular reflex. The optic discs were pale and cupped. An EEG recording demonstrated a background of alpha and some theta waves. Nerve conduction studies revealed evidence of a peripheral neuropathy mainly affecting the sensory nerves. A cerebrospinal fluid examination for IFN-α was normal (21 U/mL) (white cell count not recorded).

Further assessment at age 7 years revealed an estimated intelligence quotient of 60, unchanged features of spasticity and a head circumference continuing along the 50th centile. He had never experienced seizures. Review of his results revealed an intermittent mild elevation of liver enzymes (in the face of negative investigations for infectious causes of hepatitis), and abdominal ultrasound at this time showed mild hepatosplenomegaly. Chromosomal examination from peripheral blood lymphocytes was 46,XY and mutation analysis of the AGS1–4 genes was normal. PCR amplification of exons 1–13 of SAMHD1 failed repeatedly using DNA from this child, in spite of good amplification of exons 14, 15 and 16 using the same DNA, and amplification of parental and control DNA for all exons of SAMHD1. These find-
ings were consistent with a homozygous deletion of exons 1–13 in the affected child. This finding was confirmed by sequencing across the deletion using 5′ and 3′ primers situated upstream of exon 1 and within intron 13–14 respectively (see Fig. 7). He died at the age of 9 years because of gastroenteritis.

Patient 2
Patient 2 is the only daughter of healthy, consanguineous Egyptian parents. Family history was negative for a history of chilblains, mental retardation or epilepsy. This pregnancy was preceded by a single intrauterine foetal death at 36 weeks gestation. She was delivered vaginally weighing 1500 g (−3.7 SD) at 38 weeks gestation. Her birth length and head circumference were not recorded. There were no immediate perinatal problems. However, irritability and frequent crying were reported from soon after birth. At age 6 months she experienced generalized tonic-clonic seizures characterized by up to 5 seizures per day showing some response to sodium valproate and lamotrigine. Cranial CT performed at this age showed brain atrophy and periventricular and basal ganglia calcification and scattered calcification in the white matter (Fig. 4). At the age of 18 months the patient developed skin lesions that started on the toes and to lesser extent on the hands and the ears. These skin lesions were exacerbated by exposure to cold. The affected areas were erythematous and swollen. These lesions healed to leave circumscribed scaly erythematous plaques (Fig. 5). This process lasted for at least 3 months. The affected areas never return to normal. At age 24 months she was unable to control her head, language was absent and she smiled only occasionally. She was non-dysmorphic. On clinical examination at the age of 2½ years her weight, length and head circumference were 7 kg (−3.9 SD), 70 cm (−4.8 SD) and 39.5 cm (−6 SD), respectively. The TORCH screen was negative. Between 3 and 20 months of life she experienced episodes of sterile pyrexia, approximately once a week, lasting 2 days at a time. Over the first 2 years of life she devel-
The 2 children described here demonstrate a clinical picture consistent with AGS. Patient 2 showed an early onset encephalopathy, microcephaly, seizures, hepatosplenomegaly and high IFN-α in the CSF. These manifestations fit well with the neonatal form of AGS as proven by the finding of a homozygous mutation in TREX1. Patient 1 shows glaucoma, chilblains, intermittent sterile pyrexias and hepatomegaly, all well recognized features of AGS [4, 14, 22]. Additionally, he demonstrates typical intracranial calcification. Mild developmental delay is fully compatible with the diagnosis of AGS, and normal IFN-α titre at age 5 years is unsurprising. His diagnosis was confirmed by defining a homozygous deletion of exons 1–13 of SAMHD1.

The similarity of the severe skin lesions to those described in chilblain lupus, and the recognition that a disturbance of IFN-α metabolism is likely central to the pathogenesis of both AGS and juvenile systemic lupus erythematosus (JSLE), led us to consider JSLE in the differential diagnosis of our 2 patients. However, each disorder has its distinct diagnostic criteria. The absence of appropriate immunological markers and lack of increased mucin on Alcian blue stain (a diagnostic sign that is considered to apply to all stages and forms of cutaneous LE) in the 2 patients described here, provided evidence against this diagnosis [2]. It is of note that the histopathology of chilblains in AGS patients in previous reports has not drawn a uniform picture (Table 1). Kolivras et al. [14] described a child with chilblains demonstrating epidermal necrosis with intraepidermal bulla formation, interface dermatitis, lymphocytic vasculitis with fibrinoid necrosis and thrombi formation, both superficial and deep dermal lymphocytic infiltrate and lymphocytic eccrine hidradenitis on histopathology. Meanwhile, Dale et al. reported hyperkeratotic epidermis with spongiosis, liquefactive degeneration of the basal layer and marked papillary tip oedema [8]. Furthermore, Juern et al. [13] showed basal vacuolization of the epithelium, necrotic keratinocyte surfaced by a parakeratotic scale, perivascular lymphocytic infiltrate and thrombi formation. Our patients demonstrated thrombosis of the superficial dermal vessels and extensive fat necrosis with hyalinization but negative immunofluorescence and ANA. In view of the proposed immunological basis of AGS, discordance for immunological markers, Alcian blue and the deposition of IgM deposits along the basement membrane is of particular note. As has been similarly reported in SLE [29], it is possible that there is a correlation between the findings of positive immunofluorescence with the detection of antinuclear antibodies in the serum. More generally, the difference in appearance of the histopathology of AGS-related skin lesions could relate to the stage and severity of the disease [2].

The typical histopathological changes seen in chilblain lupus include dermal edema, keratinocyte necrosis, and a deep dermal lymphocytic infiltrate particularly prominent around vessels and eccrine glands [11, 12]. Thrombosis of the superficial dermal vessels observed in our 2 patients has been similarly reported in some cases with chilblain lupus [7, 12]. The observation of thrombi formation with associated degenerative changes (hyalinization) adds weight to the suggestion that AGS may be a microangiopathy [3, 21]. However, it is not clear if the underlying primary change is a primary vasculopathy or an inflammatory process that secondarily induces moderate vascular changes. In conclusion, the 2 patients described here illustrate the importance of chilblain lesions as a diagnostic sign in AGS, and highlight the potential interest of better defining the histopathology of AGS-related skin disease.
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Table 1

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<th>Table 1</th>
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