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CME REVIEW

PLAID: a Syndrome of Complex Patterns of Disease and Unique Phenotypes

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Abstract PLCG2 associated antibody deficiency and immune dysregulation (PLAID) is a complex dominantly inherited disease characterized almost universally by cold urticaria, and variably by recurrent bacterial infection, autoimmunty and skin granuloma formation. Several striking phenotypes can emerge from this disease, and the pathophysiology leads to a complex mix of loss and gain of function in cellular signaling. This review discusses the key phenotypic characteristics and pathophysiologic observations seen in PLAID, and contrasts PLAID to several related disorders in order to best contextualize this fascinating disease.

Keywords Cold urticaria · antibody deficiency · granuloma · PLAID syndrome

Cold urticaria is a common physical urticaria typically characterized by classic-appearing hives elicited by contact with cold material. The response is rapid—with symptom onset within minutes, as is the resolution upon warming, although prolonged systemic cold exposure can lead to anaphylaxis. The onset of responsiveness to cold tends to happen in the second or third decade of life and can resolve after years of symptoms. The gold-standard for diagnosing this curious disorder is the elicitation of a hive after exposure to an ice cube. Little is known regarding etiology, except that serum transfer from affected individuals can lead to cold induced hives in unaffected recipients, and family history of atopy, although not cold-induced atopy, is frequently seen in some populations [1].

Familial cold urticaria was commonly used as a term to describe patients with FCAS due to NLRP3 mutations which usually lead to an excess of IL-1 production. NLRP3 mutations can also lead to other autoinflammatory conditions such as Schnitzler's syndrome, Muckle-Wells Syndrome, NOMID and others. The cold-induced "urticaria" observed in those patients is actually a neutrophilic infiltrate unrelated to mast cell degranulation, and is also associated with fever and inflammation. The disorder is inherited dominantly and symptoms were often triggered by cold exposures hours earlier [2]. Delayed cold urticaria, which appears clinically more similar to typical cold urticaria except that symptom onset was hours after cold exposure, had also been described to be inherited in a dominant fashion [3]. Ghandi et al. then described an immediate cold urticaria syndrome which was also inherited dominantly [4]. Mast cell degranulation was indeed seen in affected patients' cold-exposed skin. In contrast to typical cold urticaria, the syndrome seen in Ghandi et al. was characterized by urticaria from birth which did not resolve, a tendency to react to evaporative cooling more than contact with cold objects, and a negative ice cube test.

Subsequently, PLAID (PLCG2 associated antibody deficiency and immune dysregulation) was discovered after investigating an index patient who had diffuse granulomatous dermatitis which gradually worsened from birth [5].

In addition to the granulomatous rash, further history showed that the index patient and other family members had other symptoms, inherited in an autosomal dominant fashion, the most common of which was an allergic reaction to cold.

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This index family was then compared to two additional families, some of members of whom were described in Ghandi et al., and a broad spectrum of disease was revealed [5, 6].

All patients with PLAID have an urticarial reaction to cold from infancy, including several patients who reported to having prolonged cyanosis when not placed rapidly under a warmer after birth. One patient was noted to first have symptoms when placed in a swing—which generated a cool draft.

Evaporative cooling elicited the symptoms—breezes or exposure to air conditioning while perspiring were commonly described triggers, and patients had negative ice cube challenges. Cold swimming pools could trigger symptoms, and syncope was reported in situations of prolonged systemic cold exposure. Patients are more likely to have an erythematous, pruritic, localized rash in response to evaporative cooling which was not always raised, unlike typical hives.. Eating cold foods such as ice cream can trigger of burning sensations in the throat or retrosternal regions, however unlike food-induced anaphylaxis this reaction does not progress to throat closure or other systemic responses [4].

Two distinct cutaneous findings can occur in PLAID in addition to the acute urticarial responses. In a subset of patients, a blistering rash almost resembling a burn developed within the first few days of life at the tip of the nose, ears and fingers. In most of the patients in whom the rash appeared, there was spontaneous resolution. In a few, the rash actually worsened over time, and lead to soft tissue destruction of ear and nose cartilage, with sparing of axillary folds and other warmer areas of skin. In others who had the self-resolving neonatal rash, isolated granulomatous patches were developed later in life. Histopathological examination led to the diagnosis of sarcoidosis in at least one patient due to the presence of non-caseating granulomatous dermatitis, but there was little evidence suggest a clear etiology. ACE levels were all normal in PLAID patients, with and without granulomata [6].

Patients with PLAID have a high frequency of positive anti-nuclear antibodies—up to 2/3 of the patients, while a number have clinically relevant autoimmunity in the form of autoimmune thyroiditis and vitiligo. Infectious phenotypes, when present include recurrent sinopulmonary infections varying from frequent colds and pharyngitis starting in childhood to the requirement of IVIG to treat recurrent pneumonias and bronchiectasis. Early-onset shingles and onychomycosis was noted in several patients as well [5].

Aside from the urticaria, the other phenotypes were quite variable—multiple affected patients reported that cold-induced urticaria was their only symptom. Despite the heterogeneity of symptoms, several laboratory measures were more consistent. In addition to the positive ANA, almost all patients had low serum IgM and circulating switched memory B-cells (IgM-, IgD- CD27+). Many patients also had low IgA, and poor antibody responses to pneumococcal vaccines, as well as low or low-normal NK cells. CRP and ESR were elevated in the index patient with severe granulomata but this was not seen in any others [5]. In addition, cold agglutinins and cryoglobulins, seen in other states cold-induced inflammation, were universally negative.

Heterozygous genomic deletions in PLCG2 are responsible for the majority of PLAID patients' disease. Phospholipase C gamma 2 catalyzes the hydrolysis of PIP2 to IP3 and DAG in response to receptor ligation in a variety of cell types. IP3 then serves as a second messenger to release calcium from the endoplasmic reticulum and continue the cellular activation. While PLCγ1, a structural and functional homolog, is more ubiquitously expressed, PLCγ2 expression is largely limited to lymphoid and myeloid cells except for T-cells [7]. Deletion of *plcg2* in mice leads to poor calcium flux, poor long-term B-cell memory formation, the reduction of IgM, and several subclasses of IgG [8]. NK cell function is also impaired [9], as is B-cell receptor editing [10]. Interestingly, two different mouse strains harboring *plcg2* gain of function mutations have been shown to develop dermatitis, autoinflammation and other phenotypes including, quite interestingly, skin inflammation which localizes to colder areas of the mouse body surface [11, 12]. Patients with PLAID have phenotypes predicted to be due to both gain and loss of PLCG2, and as such, the mechanism by which PLAID-associated mutations lead to disease is complex. Most affected patients have a several kilobase genomic deletion spanning parts of an autoregulatory cSH2 domain in PLCG2. This cSH2 domain normally prevents enzymatic activity, and, upon receptor ligation, is thought to be displaced, revealing the active site of the enzyme [7]. Given the structural prediction, it was therefore not surprising that these deletions render the protein constitutively active in certain in vitro transfection conditions [5]. However, primary cells from the patients paradoxically have an anergic phenotype [5] similar to that seen in plcg2 null mice, when activated at body temperature. B-cell and NK cell activation were impaired, while T-cells, which do not express significant levels of PLCγ2, did not have a signaling defect. The loss of receptor-mediated responsiveness in PLCγ2 expressing lymphocytes may be due to feedback inhibition secondary to the chronic activation, or to a direct role for the deleted regions in forming the signalosome necessary for normal receptor signal transduction [13].

The cold urticaria in these patients likely results from the fact that mast cells expressing the mutant PLCG2 spontaneously activate when exposed to lower temperatures in the absence of any antigen [5]. The temperatures which lead to activation in vitro are easily achieved in the surface of the skin with even mild cooling. It is not understood how the ice cube test could be negative in most PLAID patients, despite responses to evaporative or systemic cooling, nor is the molecular mechanism for how the cold immediately induces activation in PLCG2 mutated patients. The complex intrinsic signaling abnormalities likely lead to temperature responses

requiring a very narrow range, combining the inhibitory and excitatory states seen in cells from these patients.

Because the neonatal rash occurs in the coldest areas of the body surface, and the prolonged granulomatous rash seen in the severe cases spared warmer areas of the skin, it is quite possible that other cell types may be activated by subtle drops in skin temperature in a more chronic fashion leading to the neonatal and chronic inflammation. Consistent with that clinical observation, neutrophils and monocytes from PLAID patients showed marked cold-induced activation. Furthermore it was not clear that neutrophils could produce superoxide in response to stimulation over and above the basal activation seen, making it possible that other neutrophil defects, in addition to cold-induced activation, could contribute to granuloma formation. It should be noted, however that the cold-induced activation of neutrophils and monocytes, as well as B-cells, was present in all patients, whether a granuloma was present or not [5, 6]. Additional factors must modify the risk for granuloma formation, be they external temperature exposure variation, other intrinsic environmental exposures, or genetic modifiers.

Several families appear to have PLAID phenocopy without a detectable PLCG2 deletion or mutation [4, 6]. These patients' phenotypes suggest that the fascinating temperature-induced activation coupled with defective lymphocyte responses may be achievable through other genes in the signaling pathway, such that negative PLCG2 sequencing can no longer be assumed to be definitive in ruling out a PLAID-like disease.

Treatment of PLAID patients centers around avoidance of evaporative or systemic cooling—this includes warming rapidly after showers, toweling off sweat during and after exercise, avoiding drafts whenever possible and avoiding cold pools. Short and long-acting antihistamines can be effective as well. While the natural history of PLAID is limited to the 40–50 patients identified so far, it does not appear that the urticarial symptoms change much over time, rather affected individuals become more and more adept at avoiding the triggers. Otherwise healthy patients should be carefully monitored for changes in infection patterns, as CVID symptoms emerged only later in life in several patients. For those patients, the antibiotic prophylaxis or IVIG was determined by infectious history. The laboratory abnormalities are not as helpful, since immunoglobulin and specific antibody responses were so impaired in many otherwise asymptomatic patients. In the future, it may be possible to use PLCγ2 inhibitors to restore normal function at body temperature and prevent spontaneous activation in the cold.

It should be mentioned that a heterozygous missense point mutation in PLCG2 has been subsequently identified to cause APLAID (Autoinflammatory PLCG2 associated antibody deficiency and immune dysregulation). APLAID was seen in a father and daughter early life onset of skin inflammation and granulomata, uveitis, colitis, lung inflammation (interstitial pneumonitis with respiratory bronchiolitis), and recurrent bacterial and viral sinopulmonary infections [14]. Aspergillus infection of the lung has been noted in one of the patients. Unlike PLAID patients, cold urticaria was not observed in either patient, and cellular signaling in B-cells and cells transfected with the mutant was enhanced at body temperature, with no response to cold. The skin lesions resembled sterile cellulitis, but granulomata of unknown etiology were also noted. Like other autoinflammatory diseases, symptoms have waxed and waned over the patients' lifetime. Similar to PLAID patients, both APLAID patients had low or low-normal serum IgA and IgM levels, poor responses to pneumococcal vaccine and nearly absent class-switched B-cells. However unlike in PLAID, the APLAID patients did not have substantial autoantibody formation. Inflammatory markers such as CRP, ESR and others were normal. Why the point mutations in the same region lead to only minimal clinical overlap with the deletions seen in PLAID patients has yet to be understood.

Summary

Cold-induced allergic symptoms can be inherited in an autosomal dominant fashion and leads to distinct clinical phenotypes which can distinguish these patients from those with typical cold urticaria, and those with cold-induced autoinflammatory disorders. The mutations in PLAID lead to an intrinsic cold-induced activation which, depending on cell type, can lead to a variety of acute or chronic cold-induced phenotypes, including urticarial and granuloma. At the same time, a complex signaling defect exists, since at physiologic body temperature, signaling is impaired. This monogenic disease of atopy opens insight into mast cell and other leukocyte signaling and function, granuloma formation, and raises the notion that some mutations can lead to mendelian inheritance of acquired cold responsiveness in proteins not previously associated with cold responsiveness.

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