



الأكاديمية الجزائرية لعلوم أمراض الحساسية
Académie Algérienne d'Allergologie

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ARTICLE ORIGINAL

Unraveling a Complex Pediatric Food Allergy: CMPA, Alpha-Gal, and PR-10-Mediated PFAS

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MOTS CLÉS

Allergie aux protéines
du lait de vache

Syndrome pollen-
aliment médié par les
PR-10

Sensibilisation à
l'alpha-gal

Diagnostics
moléculaires (CRD)

Réactivité croisée

Polyallergie
pédiatrique

Résumé

Introduction : Les polyallergies pédiatriques complexes impliquent souvent des sensibilisations primaires chevauchantes et des mécanismes de réactivité croisée, rendant le diagnostic et la prise en charge particulièrement difficiles. Les diagnostics moléculaires fondés sur les composants (CRD) améliorent considérablement la précision diagnostique dans ces situations.

Description du cas : Nous décrivons un enfant présentant un phénotype allergique exceptionnel associant une allergie sévère aux protéines du lait de vache (APLV) médiée par les IgE, une sensibilisation à l'alpha-gal et un syndrome pollen-aliment médié par les protéines PR-10. Les CRD réalisés à l'âge de 3 puis 5 ans ont montré des taux élevés et persistants d'IgE dirigées contre le lait entier et la caséine (jusqu'à 78 kUA/L), une réactivité étendue aux protéines PR-10 (rBet v 1, rPru p 1, rMal d 1, rCor a 1, rGly m 4 toutes >100 kUA/L) ainsi qu'une positivité pour l'α-Gal (3,6 kUA/L). Cliniquement, l'enfant présentait des réactions systémiques après ingestion de lait de vache, un syndrome d'allergie orale aux aliments contenant des PR-10, et un épisode d'anaphylaxie sévère après consommation de yaourt et de pêche. La prise en charge a reposé sur l'éviction stricte du lait et du bœuf ainsi que l'instauration d'une immunothérapie spécifique au pollen de bouleau.

Conclusion : Ce cas illustre le rôle essentiel des CRD pour démêler des profils de sensibilisation complexes, distinguer une allergie alimentaire primaire d'une réactivité croisée induite par les pollens et guider une prise

KEYWORDS

Cow's milk protein allergy

PR-10-mediated pollen-food allergy syndrome

Alpha-gal sensitization

Component-resolved diagnostics

Cross-reactivity

Pediatric polyallergy

en charge personnalisée. L'association d'une APLV sévère, d'un PFAS médié par les PR-10 et d'une sensibilisation à l'alpha-gal souligne l'importance d'une évaluation individualisée dans les polyallergies pédiatriques.

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Abstract

Background: Complex pediatric polyallergy often involves overlapping primary sensitizations and cross-reactive pathways, making diagnosis and management challenging. Component-resolved diagnostics (CRD) significantly improves diagnostic accuracy in such settings.

Case Presentation: We report a child with an uncommon triple-allergy phenotype combining severe IgE-mediated cow's milk protein allergy (CMPA), alpha-gal sensitization, and PR-10-mediated pollen-food allergy syndrome (PFAS). CRD performed at ages 3 and 5 revealed persistently high whole-milk and casein-specific IgE levels (up to 78 kUA/L), extensive PR-10 reactivity (rBet v 1, rPru p 1, rMal d 1, rCor a 1, rGly m 4 all >100 kUA/L), and positive α-Gal (3.6 kUA/L). Clinically, the child experienced systemic reactions to cow's milk, oral allergy syndrome to PR-10-containing foods, and a severe anaphylactic episode after ingestion of yogurt and peach. Management included strict exclusion of cow's milk and beef and initiation of birch pollen allergen immunotherapy. Follow-up over nine months showed good clinical stability.

Conclusion: This case illustrates the pivotal role of CRD in disentangling complex sensitization networks, distinguishing primary food allergy from pollen-driven cross-reactivity, and guiding precision-based management. The coexistence of severe CMPA, PR-10-mediated PFAS, and alpha-gal sensitization underscores the importance of individualized assessment in pediatric polyallergy.

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Introduction :

Complex polyallergies in children represent a growing challenge in clinical immunology, where multiple coexisting sensitizations and extensive cross-reactivity obscure the underlying immune mechanisms [1,2]. Among these conditions, cow's milk protein allergy (CMPA) stands out as the leading food allergy in Tunisia [3], which likely reflects the broader North African epidemiological pattern. It is a clinically significant IgE-mediated allergy of early childhood, frequently associated with severe systemic reactions and a substantial nutritional and psychosocial burden [4,5]. In contrast, pollen-food allergy syndrome (PFAS), characteristic of the classic northern Mediterranean pattern, is most commonly associated with sensitization to PR-10 proteins (Bet v 1 homologues). It represents a prototypical form of cross-reactivity between inhalant and food allergens and typically presents with milder oropharyngeal symptoms [6–9].

Disentangling such overlapping allergic pathways remains difficult when relying solely on extract-based diagnostic tools. These conventional assays cannot reliably distinguish primary sensitizations from cross-reactive IgE responses, which limits diagnostic precision and therapeutic decision-making. The emergence of molecular allergology—particularly component-resolved diagnostics (CRD)—has enabled unprecedented resolution in the characterization of sensitization profiles. By identifying IgE responses to individual allergenic molecules, CRD refines diagnostic accuracy, predicts clinical relevance, and guides personalized management [10–13]. Here, we report a unique pediatric case marked by severe IgE-mediated cow's milk protein allergy, concomitant alpha-gal sensitization, and PR-10-mediated PFAS. CRD played a central role in delineating the dual molecular mechanisms that explained the patient's complex clinical phenotype. This case exemplifies the translational value of

molecular allergology in elucidating intricate sensitization networks and optimizing precision-based management in pediatric allergy.

Case Report

A 3-year-old boy, born at term with normal growth and psychomotor development, was referred for evaluation of suspected food allergy. Family history was positive for atopy: his mother had allergic asthma and house dust mite-induced allergic rhinitis. The child had been mixed-fed from the age of two months and was fully vaccinated. Beginning at six months of age, he developed recurrent episodes of urticaria treated with antihistamines, episodic wheezing with cough, and gastrointestinal manifestations such as vomiting and loose stools, typically occurring within minutes to hours after ingestion of cow's milk or dairy products. Physical examination between episodes was unremarkable, except for mild xerosis, with no evidence of malnutrition or respiratory compromise.

Skin prick testing (SPT) showed a strongly positive wheal to cow's milk extract (Figure 1). Serum allergen-specific IgE (sIgE) measured by ImmunoCAP® fluoroimmunoassay (Phadia™ 100, Thermo Fisher Scientific®, Uppsala, Sweden), revealed elevated IgE levels to whole cow's milk ($f_2 = 56.9$ kUA/L) and its molecular allergenic components: β -lactoglobulin (nBos d5 = 13.4 kUA/L), α -lactalbumin (nBos d4 = 5.9 kUA/L), and casein (nBos d8 = 62 kUA/L). All specific IgE measurements are summarized in Table 1.

The marked sensitization to the thermostable casein fraction supported a diagnosis of persistent IgE-mediated CMPA, predicting reactivity even to baked milk. A strict milk-free diet and an emergency action plan including self-injectable epinephrine were prescribed.

At age five, after residing in Sweden for two years, the patient re-presented during a visit home with persistent allergic rhinitis and recurrent episodes of urticaria, as well as gastrointestinal and respiratory symptoms triggered by multiple foods. Ten minutes after consuming yogurt and a quarter of a peach, he developed acute angioedema requiring intramuscular epinephrine and emergency care. Given the severity of this IgE-mediated event (anaphylaxis, Grade IV), SPT was deferred, an avoidance diet was initiated, and a comprehensive panel of serum sIgE measurements was prescribed. Because of respiratory involvement, Phadiatop™ testing was performed to screen for inhalant allergen sensitization.

The allergy-focused history revealed prior episodes of oral allergy syndrome to apple and tree nuts; a first-ever known ingestion of peach at the time of the acute reaction; and a prior symptomatic episode after rare beef consumption. Based on these findings, repeat testing for cow's milk proteins, soybean, and beef was performed to

evaluate potential cross-reactivity. Additional testing for apple, hazelnut, and peach was guided by the clinical history. Considering the patient's frequent outdoor activities with potential tick exposure, alpha-gal syndrome was evaluated as well. Although no clear tick bites were documented, testing for α -Gal was warranted to exclude delayed mammalian meat allergy.

In the context of deferred skin testing, Phadiatop™ was complemented with the most prevalent inhalant allergens in Tunisia and birch pollen, given the classic birch-apple association and the patient's recent residence in Sweden.

Repeat testing confirmed persistent CMPA, with whole cow's milk sIgE of 59 kUA/L. Molecular analysis again showed sensitization to β -lactoglobulin (13.4 kUA/L), α -lactalbumin (6 kUA/L), and casein (78 kUA/L), consistent with severe and thermostable profile. Sensitizations to soybean and beef were detected: whole soybean sIgE was 27 kUA/L, Gly m4 (PR-10) >100 kUA/L; beef sIgE was 2.38 kUA/L; and α -Gal (Galactose- α -1,3-galactose) was 3.6 kUA/L. These findings supported continued clinical vigilance regarding potential mammalian meat reactions.

Food allergen testing revealed marked sensitization to peach, with whole allergen sIgE of 18.5 kUA/L, PR-10 component rPru p 1 >100 kUA/L, with negative IgE to LTP (rPru p 3 <0.1 kUA/L) and profilin (rPru p 4 <0.1 kUA/L).

Similarly, sensitization to apple was confirmed with whole allergen IgE of 12.8 kUA/L and PR-10 component rMal d 1 >100 kUA/L. Hazelnut sensitization was also present, with whole allergen IgE >100 kUA/L and PR-10 component rCor a 1 >100 kUA/L.

Taken together, these findings strongly supported a PR-10-mediated PFAS rather than an LTP-driven systemic allergy and emphasized the importance of CRD in defining the patient's molecular sensitization profile.

Phadiatop™ was positive. Extended aeroallergen testing revealed sensitization to olive pollen ($t_9 = 8.9$ kUA/L) and birch pollen (rBet v 1, $t_{215} >100$ kUA/L). CRD confirmed broad IgE reactivity to PR-10 homologues: rBet v 1, rPru p 1, rCor a 1, rMal d 1, and rGly m 4 (all >100 kUA/L), with negative IgE to LTPs, profilins, and gibberellin-regulated proteins (GRPs).

This molecular pattern indicated a PR-10-driven sensitization consistent with oral allergy syndrome to fruits and tree nuts, alongside systemic reactions to cow's milk. Given the patient's lifestyle and potential tick exposure, alpha-gal sensitization was considered clinically relevant, even without documented tick bites. Ongoing clinical surveillance was recommended. All sIgE measurements are detailed in Table 2.

Allergic Phenotype and Management

This molecular profile established a dual allergic phenotype:

- Persistent, primary IgE-mediated CMPA, associated with mild cross-reactivity to beef (α -Gal = 3.6 kUA/L).
- PR-10-related PFAS secondary to birch pollen sensitization, explaining oral and gastrointestinal reactions to PR-10-containing foods (peach, apple, hazelnut, soybean).

The patient was started on birch pollen allergen immunotherapy to target inhalant sensitization and mitigate PR-10-mediated cross-reactivity. Dietary recommendations included complete elimination of cow's milk and beef, with cautious reintroduction of PR-10-containing fruits only when thermally processed. During a 9-month follow-up, the patient remained clinically stable with no recurrence of symptoms. This case illustrates the critical value of component-resolved molecular diagnostics in disentangling complex sensitization patterns, distinguishing true primary food allergy from pollen-related cross-reactivity, and guiding precision-based management in pediatric polyallergy.

Discussion

Polyallergy in pediatric patients represents a multifaceted immunologic challenge in which primary sensitizations, secondary cross-reactivity, and diverse clinical manifestations interact to produce complex and evolving phenotypes. In this case, primary CMPA coexisted with PR-10-mediated PFAS, illustrating the intricate overlap between systemic IgE-mediated food allergy and pollen-related cross-reactive responses. PFAS arises from secondary IgE cross-reactivity between structurally homologous proteins shared by pollens and plant-derived foods. In Northern and Central Europe, birch pollen sensitization to Bet v 1 is the classical trigger and accounts for cross-reactive responses to apple (Mal d 1), hazelnut (Cor a 1), and peach (Pru p 1) [1,8,9,12,14,15]. Epidemiologic data indicate that 5–10% of school-age children in endemic regions experience PFAS, with prevalence increasing to 30–50% among birch-sensitized children. In Sweden, PFAS affects 70% of individuals with birch pollen allergy and 19% of those sensitized to other pollens. In the United Kingdom, prevalence ranges from 17% in children younger than five to 78% in those older than ten. Korean studies report a prevalence of 42.7% in pollen-allergic children and up to 36.6% in preschoolers sensitized to birch pollen [14,16–18]. These observations highlight the strong link between birch sensitization and secondary food allergy in pediatric populations, emphasizing the utility of molecular allergology in characterizing sensitization patterns and guiding individualized management. To date, no peer-reviewed epidemiological study has specifically evaluated the prevalence of PR-10 (Bet v 1)-related PFAS in North African countries, where birch sensitization

is rare. No pediatric cohort in the region has applied CRD to quantify PR-10-mediated PFAS. In Tunisia, pollen sensitization profiles are dominated by herbaceous and olive pollens rather than birch [19,20]. Data from southern Europe similarly indicate lower PFAS prevalence or involvement of alternative cross-reactive allergen patterns compared to Northern Europe [21]. In fact, the prevalence of PFAS in the Mediterranean region, where birch pollen is largely absent, is estimated at approximately 20% [22]. Reported pediatric PFAS prevalences include 35.9% in an Italian cohort, 27% among Italian children with seasonal allergic rhinitis [23,24], 29.7% in Croatia [25], 16% in French children with asthma [26], and 3.3% in Turkish children with respiratory allergies [27]. These variations highlight the need for region-specific studies to better define local PFAS prevalence and molecular profiles in Mediterranean populations.

The mechanistic basis of PR-10 cross-reactivity lies in the conserved tertiary structure of Bet v 1-related proteins [15]. These proteins share a hydrophobic pocket and surface-exposed IgE epitopes recognized by B cells, while T-cell recognition occurs through linear epitopes with variable sequence identity. This dual epitope architecture may contribute to epitope spreading and amplification of clinical symptoms.

In this case, IgE recognition of Bet v 1 and multiple PR-10 homologues explained the constellation of symptoms and justified birch allergen immunotherapy (AIT), which may modulate B- and T-cell responses, reduce epitope spreading, and mitigate PFAS symptoms. The thermolability of PR-10 proteins explains why symptoms are generally restricted to raw foods, in contrast to heat-stable proteins such as casein or LTPs, which can induce systemic reactions [28,29]. PFAS typically presents as oral allergy syndrome (OAS), with localized oropharyngeal symptoms such as itching or mild angioedema [8,30,31]. However, systemic reactions do occur: up to 20% with Rosaceae fruits and 40–50% with soybean, underscoring the need for vigilance even with labile allergens [32]. Recent evidence suggests that PR-10 IgE profiles and quantitative IgE thresholds can differentiate silent sensitization from clinically relevant phenotypes and help predict the risk of systemic reactions, including anaphylaxis. Elysuitina et al. [33] demonstrated that asymptomatic children exhibit significantly lower IgE to Bet v 1 and PR-10 allergens than symptomatic patients. A threshold of 6.8 ISU for Bet v 1-specific IgE was strongly associated with OAS. Broader PR-10 reactivity correlated with multimorbidity. Similarly, Litovkina et al. [34] showed that symptomatic patients have significantly higher IgE levels and broader reactivity to PR-10 allergens, with a cutoff of 70 ISU differentiating isolated OAS from systemic manifestations.

These findings align with our case, in which high-magnitude PR-10 sensitization was associated with clinically significant OAS and an acute angioedema episode. While PR-10 IgE titers can aid risk stratification, symptom severity remains multifactorial and influenced by allergen dose, cofactors, and individual immunologic parameters. Primary CMPA results from IgE sensitization to heat-stable cow's milk proteins, particularly casein (Bos d 8), which predicts persistent allergy and potential anaphylaxis [35].

In this patient, markedly elevated casein-specific IgE indicated high risk for reactions to both raw and heated milk. Specific IgE levels are key predictors of CMPA persistence and severity, as shown in Tunisian and European cohorts [3,36,37]. A Tunisian study identified thresholds of 4.2 kU/L for whole milk and 0.37 kU/L for casein as predictive of persistent CMPA [3]. German data indicate faster tolerance acquisition in children with milk IgE <5 kU/L [36]. Payot et al. similarly found that tolerant children had significantly lower IgE levels to whole milk and casein [37]. Although such thresholds vary by region and technique, levels above 5 kU/L often predict persistent allergy [38,39].

In our patient, milk-specific IgE at 59 kUA/L and casein-specific IgE at 78 kUA/L were highly suggestive of persistence. Beef allergy, though uncommon in the general pediatric population (0.3%) [40], coexists in 13–20% of infants with CMPA and is associated with cross-reactivity to bovine proteins such as bovine serum albumin [41,42]. In our patient, sensitization to beef and α -Gal required careful dietary counseling given the potential for delayed mammalian meat reactions.

The coexistence of severe CMPA and PR-10-mediated PFAS with distinct molecular profiles underscores the importance of CRD in evaluating complex pediatric allergy. CRD allows precise identification of the responsible allergenic components, distinguishing primary systemic allergens from labile cross-reactive proteins. This distinction is essential for risk assessment, dietary recommendations, and therapeutic decision-making. One major advantage of CRD is risk stratification. Heat-stable molecules (e.g., casein, LTPs) are associated with systemic reactions, whereas PR-10 allergens generally induce localized OAS. This molecular precision guides both acute management and preventive strategies [12,43].

CRD also enables targeted nutrition management, avoiding unnecessary restrictions and supporting safe reintroduction of tolerated foods such as cooked fruits in PR-10-mediated PFAS [44–46]. CRD additionally guides AIT decisions, as in this case where birch pollen was identified as the primary sensitizer [47–50]. Finally, CRD facilitates longitudinal monitoring by tracking evolving sensitization patterns and preventing

misinterpretation of extract-based cross-reactivity [11,51–53].

In this child, CRD clarified a dual phenotype: persistent, systemic CMPA requiring strict avoidance of cow's milk and beef, and PR-10-mediated PFAS characterized by high-magnitude sensitization, supporting birch AIT and cautious consumption of cooked fruits. This case illustrates the clinical utility of molecular allergology in diagnosing, stratifying, and managing polyallergic pediatric patients. Overall, CRD provides a powerful translational tool that refines diagnosis, predicts risk, and enables personalized management in complex pediatric allergy. This case highlights its added value in disentangling overlapping sensitization pathways and guiding precision-based therapeutic strategies.

Conclusion

The coexistence of severe CMPA, beef allergy, PR-10-mediated PFAS, and alpha-gal sensitization in a single pediatric patient highlights the complexity and uniqueness of this triple allergy phenotype. This case underscores the critical importance of individualized evaluation in children with multiple coexisting allergies. Component-resolved diagnostics (CRD) proved indispensable in distinguishing primary IgE-mediated sensitizations from secondary cross-reactive responses, guiding precise dietary management, informing allergen-specific immunotherapy, and enabling risk stratification for potentially severe systemic reactions. While PR-10-mediated PFAS is often perceived as mild, its clinical significance increases in the context of overlapping sensitizations, emphasizing the need for vigilant assessment. Ultimately, a CRD-guided precision medicine approach optimizes both safety and quality of life for pediatric patients with complex polyallergic profiles, illustrating the tangible translational value of molecular allergology in specialized pediatric care.)

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Table 1: Specific IgE profile at age 3 years (Whole allergen extract and component-resolved allergens)

Allergen	Type	Specific IgE (kUA/L)
Cow’s milk	Whole allergen	56.9
β-lactoglobulin (nBos d5)	Molecular	13.4
α-lactalbumin (nBos d4)	Molecular	5.9
Casein (nBos d8)	Molecular	62

Table 2: Specific IgE profile at age 5 years (Whole allergen extract and component-resolved allergens)

Allergen Category	Allergen	Type	Specific IgE (kUA/L)
Food	Cow's milk	Whole allergen	59
	β -lactoglobulin (nBos d5)	Molecular	13.4
	α -lactalbumin (nBos d4)	Molecular	6
	Casein (nBos d8)	Molecular	78
	Peach	Whole allergen	18.5
	Peach PR-10 (rPru p1)	Molecular	>100
	Peach LTP (rPru p3)	Molecular	<0.1
	Peach Profilin (rPru p4)	Molecular	<0.1
	Apple	Whole allergen	12.8
	Apple PR-10 (rMal d1)	Molecular	>100
	Hazelnut	Whole allergen	>100
	Hazelnut PR-10 (rCor a1)	Molecular	>100
	Soy	Whole allergen	27
	Soy PR-10 (rGly m4)	Molecular	>100
	Beef	Whole allergen	2.38
	α -Gal (Galactose- α -1,3-galactose)	Molecular	3.6
Respiratory	Olive pollen	Whole allergen	8.9
	Birch pollen	Whole allergen	>100
	Birch PR-10 (rBet v1)	Molecular	>100
	Cypress pollen	Whole allergen	<0.1
	Cat dander	Whole allergen	<0.1

PR-10: pathogenesis-related protein family 10; LTP: lipid transfer protein.

All other molecular components tested were negative.

Figure 1 Prick test

