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Case Presentation

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Muckle-Wells Syndrome in an Adult Chinese Female: Age, Ethnicity and Genotype Matter

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Abstract

Muckle-Wells syndrome (MWS) belongs to one of the three forms of the cryopyrin-associated periodic syndrome (CAPS). Symptom onset is reported to start at an early age and the disease is generally thought of as a paediatric condition. In this report, we describe a patient who was diagnosed in adulthood and the implications of her delayed diagnosis. To date, the factors influencing the clinical course among CAPS patients have not been well characterised due to the heterogeneity of its manifestations and the rarity of this disease. We review the literature and describe how factors such as age, ethnicity and genotype shape the clinical continuum of this disease.

Keywords: Urticaria; Muckle-Wells syndrome; Cryopyrin-associated Periodic Syndrome; Chinese; Asian; Ethnicity; NLRP3; Mutation; Genotype

Introduction

Muckle-Wells Syndrome (MWS) is a rare autoinflammatory disease belonging to one of three clinical forms of the Cryopyrin-Associated Periodic Syndrome (CAPS). The disease begins at an early age (ranging from 6 months to 6 years) and is usually thought of as a paediatric condition [1]. Given the broad spectrum of manifestations among patients with CAPS, factors determining its clinical phenotype, course and prognosis have not been well characterised in existing literature.

Case Presentation

A 44-year-old Chinese woman presented with recurrent urticaria since infancy. Urticarial attacks were exacerbated by cold and associated with fever, myalgia and arthritis. Such episodes lasted for 24 hours each time. Her history was notable for intermittent conjunctivitis and bilateral

sensorineural hearing loss, which was confirmed on audiometry 8 years prior. Her family history was unremarkable. Initial examination showed urticarial wheals over her arms and thighs **(Figure 1)**. A cold ice test performed was negative. Biochemistry was significant for raised C-Reactive Protein (CRP; 30.9 mg/L), erythrocyte sedimentation rate (ESR; 75 mm/hr) and neutrophilia (absolute count 8.9 x 103/uL). There was no renal impairment or proteinuria. Her autoimmune screen returned negative and serum protein electrophoresis showed no monoclonal band. Her cytokine profile was significant for raised IL-6 (14.2 pg/mL; upper limit of normal 5.0 pg/mL). Histology from a skin biopsy showed a dermal lymphohistiocytic infiltrate with no evidence of vasculitis. Subsequent genetic testing identified the R260W pathogenic variant (c.784C>T; p.Arg262Trp) in the NOD-like receptor 3 (NLRP3) gene. She was diagnosed with Muckle-Wells Syndrome (MWS) and commenced on anakinra 100 mg once daily. Two weeks later, she developed swelling and induration over injection sites on her thighs, consistent with delayed injection-site reactions to anakinra. She received antihistamines and prednisolone and tolerated continued treatment with anakinra. Within a month, she experienced resolution of her urticaria, fever, myalgia, arthritis and conjunctivitis **(Figure 1)**. Her CRP level normalised and ESR decreased to 34 mm/hr.

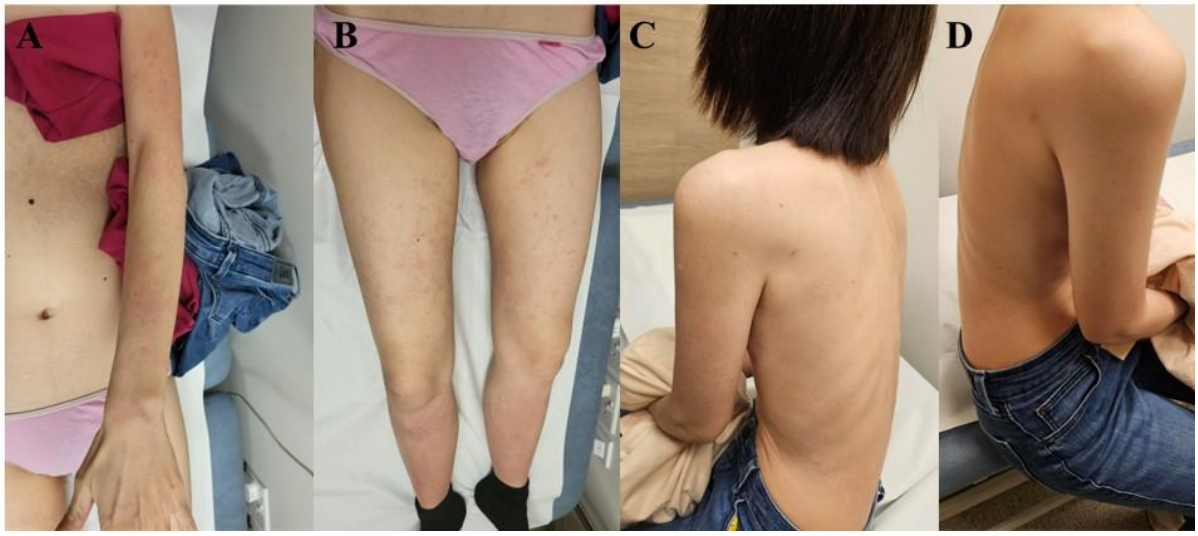

Figure 1: [A, B] Clinical photos before anakinra showing urticarial wheals over the arms and thighs [C, D] Clinical photos after anakinra demonstrating resolution of urticaria.

Discussion

Age

Febrile attacks in CAPS begin in early childhood with a median age of 0.8 years **[1]**. An onset before the age of 6 months is predictive of severe neurological complications and hearing loss **[2]**. Paediatric patients may experience more fever, rash and neurological involvement compared to adults **[3]**. Late diagnosis in adulthood entails greater morbidity, a lower quality of life and greater risks of AA amyloidosis. Due to her delayed diagnosis, our patient was unable to hold a job and she suffered from permanent hearing loss. Thankfully, she did not have amyloidosis at presentation (as evidenced by a normal renal function, absence of proteinuria or signs of peripheral neuropathy).

Ethnicity

To date, few studies have been undertaken amongst CAPS patients of Asian descent. In 2022, Zhou et al reported a higher frequency of fever among the Chinese population compared to Western populations. The same study highlighted an increased frequency of neurological involvement, severe neurological symptoms and severe musculoskeletal symptoms, but a lower frequency of ocular symptoms among the Chinese compared to Western populations [3]. Aoyama et al. did a review of 19 Japanese patients with CAPS in 2012. Overall, CAPS patients of East Asian descent had less musculoskeletal manifestations compared to Western patients [3,4]. Reports of cryopyrinopathies from the Indian subcontinent are scarce. Khemani et al. reported a case of chronic infantile neurological, cutaneous, articular syndrome in a 7-year-old Indian girl who had retinal vasculitis and a paucity of neurological signs [5]. Two other Indian patients with MWS who had overlapping features of FCAS and NOMID were reported by Abdulla et al in 2015 [6].

Genotype

Existing literature supports the association of distinct phenotypes with certain mutations, reflecting the influence of genetic background on disease course. Our patient had the R260W pathogenic variant in the NLRP3 gene. This variant is associated with a positive family history [2]. NLRP3 mutations are generally autosomal dominantly inherited but may also arise de novo. These patients should be identified early and offered genetic counselling. As our patient's parents were unaffected, it is likely that she her mutation occurred de novo. She never married and had no children. The R260W mutation is also associated with cold-triggered attacks, a trend towards symptom onset after 2 years of age and a chronic disease course [2]. Interestingly, the R260W mutation is considered a risk factor for AA amyloidosis, and this mutation is the most frequently encountered pathogenic variant among CAPS patients with amyloid kidney disease [7]. The largest retrospective study of CAPS patients to date was performed by Levy et al. [2], which examined the phenotypic and genotypic characteristics of 136 CAPS patients from the Eurofever registry **(Table 1)**. Comparatively, the genetic spectrum of CAPS amongst Asians has been less well-studied. A novel mutation, p.Leu361Trp, was reported in a Chinese patient in 2022; however, functional testing was not possible [3]. The F309S and D303N (c.907G>A; p.Asp303Asn) mutations have been reported amongst Indian patients [5,6]. F309S is associated with more severe phenotypes while D303 mutations may present with variable severities [8]. Nonetheless, these mutations are not unique to this ethnic group.

Table 1: Key genotype subgroups and associated phenotype.

Mutation	Phenotype
R260W	Median onset after 2 years, positive family history, cold-triggered attacks, chronic disease course in 42%, risk factor for AA amyloidosis
T348M	Median onset before 2 months of age, chronic disease course in 85%, hearing loss in 70%
V198M	Median onset 1.5 years, low penetrance, neurological involvement rare
A439V	Median onset 4 years, positive family history, neurological involvement rare

E311K	Median onset 2 years, high rate of hearing loss, neurological involvement rare
Q703K	Median onset 6 years, no family history, mild disease, no arthritis, neurological involvement or deafness
Rare or no mutation(s)	Onset before 6 months of age, severe neurological and musculoskeletal and ophthalmological manifestations, hearing loss

Conclusion

Urticaria in the presence of systemic symptoms should always be investigated. A diagnosis of MWS should be considered even among adults who present with suggestive clinical features, as delayed diagnosis will lead to poorer outcomes.

Age, ethnicity and genotype heavily influence the clinical spectrum of CAPS. The late age of presentation and the genetic phenotype of our patient portend a chronic disease course with high risk of AA amyloidosis. She will require lifelong anakinra and periodic monitoring for the development of amyloidosis (with regular renal function tests and urinalysis for proteinuria). Her Chinese ethnicity places her at an increased risk of developing neurological complications, and she will be monitored closely for these signs. Should she lose response to anakinra, an alternative should be offered. Tocilizumab has been employed to treat CAPS patients, with favourable response in the literature **[9]**; it may be effective in our patient, whose cytokine profiling demonstrated raised IL-6 levels. As the clinical course of CAPS patients differs according to their genetic phenotyping, we propose that genetic testing should be offered to such patients to prognosticate and guide subsequent management.

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