CASE REPORT

The Negative HLA-B*1502 Status is Not an Absolute Exclusion of Carbamazepine-induced Steven Johnson Syndrome/toxic Epidermal Necrolysis: A Pediatric Case Report

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ABSTRACT

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) represent infrequent yet severe skin and mucous membrane disorders, frequently instigated by certain medications, notably carbamazepine. Diagnostic challenges arise due to the absence of definitive laboratory assays. While the presence of the HLA-B*1502 allele is established as a predisposing factor for carbamazepine-induced SJS/TEN, instances of reaction manifestation in patients devoid of this genetic marker are documented. Essential to effective management is a comprehensive understanding of disease trajectory, precise discrimination from mimicking conditions, and prompt therapeutic intervention. This study underscores the critical importance of vigilant disease monitoring and personalized treatment approaches. Notably, this vigilance is imperative even in carbamazepine-treated patients lacking the HLA-B*1502 genotype. Additionally, the potential utility of exploring other alleles, such as HLA-B75, warrants consideration to optimize treatment strategies.
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Keywords: Steven-johnson syndrome, Toxic epidermal necrolysis, HLA B*1502, Carbamazepine, Anticonvulsant

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INTRODUCTION

Carbamazepine, a widely prescribed anticonvulsant medication in the treatment of epilepsy and other neurological disorders, has been incontrovertibly linked to severe cutaneous adverse drug reactions (SCAR), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). These dermatologic conditions, although rare, manifest with profound cutaneous involvement characterized by blistering of the skin and mucous membranes. SJS and TEN fall within the spectrum of type IV hypersensitivity reactions and share overlapping clinical features, spanning from benign urticaria to life-threatening dermatological manifestations. Distinction between SJS and TEN primarily hinges on the extent of epidermal detachment (1).

The identification of the causative agent in SCAR remains an ongoing challenge, compounded by the absence of definitive laboratory assays. While medication and infections constitute the most common triggers, the etiological underpinnings are particularly complex in the pediatric population. Of notable relevance is the HLA-B*1502 allele, which exhibits a robust association with carbamazepine-induced SJS/TEN, particularly among Asian populations, prompting recommendations for genotype screening prior to carbamazepine initiation (2).

Despite the established correlation between HLA-B*1502 and carbamazepine-induced SCAR, recent clinical observations have illuminated cases where patients lacking this genetic predisposition still develop severe reactions following carbamazepine exposure. This phenomenon underscores the nuanced nature of SCAR pathogenesis and the limitations of relying solely on genetic screening for risk assessment. Consequently, there is a critical imperative to elucidate alternative

mechanisms contributing to carbamazepine-induced SCAR, including testing for a wider genotype pool beyond HLA-B*1502 alone.

In this context, we present a pediatric case report highlighting the complexity of carbamazepine-induced SJS/TEN, wherein the absence of HLA-B*1502 did not preclude the development of severe cutaneous adverse reactions. Through this case illustration, we aim to underscore the multifaceted nature of SCAR pathogenesis and advocate for a comprehensive approach to risk assessment and management in pediatric patients treated with carbamazepine.

CASE REPORT

We present a case of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) in a pediatric patient who tested negative for the HLA-B*1502 allele. The patient, a 4-year-old boy, had been diagnosed with focal epilepsy one year prior to the current admission and had initially been receiving Syrup Sodium Valproate for seizure control. Upon confirmation of focal seizures during outpatient follow-up through electroencephalogram and a negative HLA-B*1502 test result, oral carbamazepine was initiated at 5mg/kg/day, gradually increased to 10mg/kg/day over two weeks. With the new anti-epileptic regimen, his seizures were well-controlled, occurring once a month prior to this admission.

The patient was later presented to our center with a one-week history of fever, chesty cough, and runny nose. Upon admission, he continued to experience high fever with mild respiratory distress, leading to a diagnosis of pneumonia. He was empirically treated with intravenous Cefuroxime and oral Azithromycin, and his fever and symptoms resolved by the third day of admission.

However, on the third day of hospitalization, the patient's seizure frequency increased to three times per week with similar semiology and duration. Consequently, the decision was made to increase the carbamazepine dosage to 14mg/kg/day. Within the same day of the increment of carbamazepine dose, the patient developed macular rashes on his trunk and face, accompanied by non-purulent conjunctivitis. The rash progressed rapidly, with the appearance of blisters over various body areas. Mucosa was involved, as evidenced by non-purulent conjunctivitis in both eyes. His bilateral palms and soles were swollen, although no blisters were observed at that time (Figure 1).

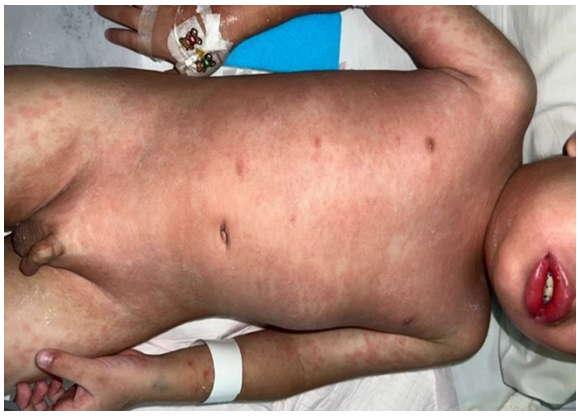

Figure 1: Well-defined pinkish to reddish macular rash spreading from his trunk to his face, ears, and inguinal area.

Upon initial assessment, the presentation resembled that of erythema multiforme, prompting the administration of a single dose of intravenous methylprednisolone at 10mg/kg/day. Concurrently, antibiotic therapy was intensified with intravenous meropenem at a dose of 40mg/kg every eight hours. However, the rash exhibited rapid progression on the subsequent day, characterized by the emergence of blisters spanning the right arm, trunk, ears, mouth, genitalia, and palms (Figure 2).

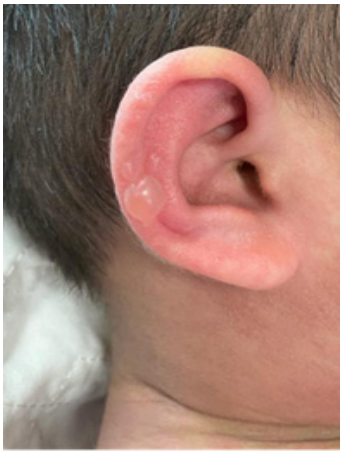

Figure 2: Blister over the ear pinna.

In light of the clinical evolution and the advancing rash, a diagnosis of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (SJS/TEN) was established, with carbamazepine identified as the suspected precipitating agent. A thorough review of the medication history was undertaken, with parental disclosure indicating sole administration of sodium valproate and carbamazepine within the preceding 12 weeks.

As the cutaneous manifestations persisted and intensified

(Figure 3), therapeutic intervention was initiated with intravenous Methylprednisolone at a dose of 10mg/kg/day and intravenous immunoglobulin at a dose of 1g/kg/day. Both modalities were administered over a three-day period. Notably, no new lesions emerged beyond the seventh day of treatment initiation. Subsequently, a gradual resolution of lesions ensued over a fifteen-day period, facilitating the patient's discharge with a tapering regimen of oral prednisolone administered at intervals of every five days. Comprehensive blood investigations are delineated in Table I.

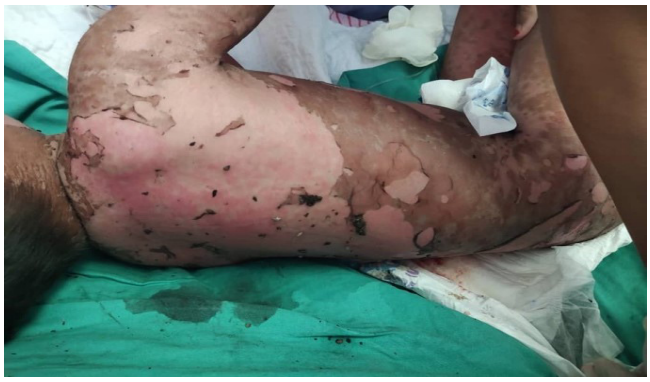

Figure 3: Epidermal detachment over Posterior torso.

Table I: Blood investigations

Test	Values	Normal range
White cell counts	7.2	4-11.50 10^9/L
Haemoglobin	12.4	10-12 10^9/L
Platelet	132	150-450 10^9/L
C-reactive protein	<2	0-0.5 mg/dL
Albumin	38.9	29-58g/L
Aspartate aminotransferase	159.4	0-31 U/L
Alanine transaminase	53.4	<30 U/L
Urea	1.7	2.1-6.5 mmol/L
Sodium	133	135-145 mmol/L
Potassium	3.8	3.5-5 mmol/L
Creatinine	48	27-62 umol/L
Mycoplasma IgM	<1:40	<1:40
Antistreptolysin O antibody	<200	</=200
Blood Culture	No growth	
Urine Candida	Positive	

DISCUSSION

During the early manifestation of the rash, differential diagnoses such as Kawasaki disease, viral exanthem, and erythema multiforme (EM) are commonly considered. However, a comprehensive understanding of the natural progression of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) is paramount for distinguishing these conditions from their mimics. The typical course of SJS/TEN involves preceding fever and symptoms resembling coryza, followed by the emergence of skin and mucosal lesions within days one to three of onset. The rash often presents as non-blanching purpuric macules, which frequently progress to blistering and sloughing off within 12 hours.

While carbamazepine is indispensable in the treatment of seizures, it is also linked to a spectrum of cutaneous manifestations, ranging from benign urticaria to potentially life-threatening hypersensitivity reactions. Notably, hypersensitivity reactions to drugs typically manifest within 2-6 weeks after exposure (3). Tangamornsuksan et al. (2013) underscored a significant association between the HLA-B*1502 allele and carbamazepine-induced SJS/TEN in Han Chinese, Thai, and Malaysian populations (4). Despite the negative HLA-B1502 status in the presented case, heightened vigilance for SJS/TEN in patients receiving carbamazepine is imperative. This vigilance facilitated prompt monitoring and subsequent elimination of exposure, alongside early initiation of immunotherapy, effectively arresting disease progression.

The cornerstone of SJS/TEN management revolves around identifying and eliminating causative agents, symptom control, and complication mitigation. To effectively address and eliminate causal factors, a thorough review of the patient's history is paramount, encompassing medication usage, potential exposure to infectious sources, and comprehensive clinical examination. Moreover, genetic testing should be considered, extending beyond the confines of HLA-B*1502 alone. Notably, recent research has identified other alleles, such as HLA-B75 and HLA-B*1521, as predisposing factors for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (SJS/TEN) (5). This comprehensive approach to genotyping allows for a more nuanced understanding of genetic susceptibility, facilitating targeted interventions and personalized management strategies.

The duration of recovery from SJS/TEN in pediatric patients is contingent upon the extent and severity of the lesions. While this report represents a single case, aggregating data from similar cases within the Malaysian context may offer insights into the prevalence and trends of HLA-B*1502-negative patients with SJS/TEN in the Malaysian populace. Such insights could inform and enhance future management strategies.

CONCLUSION

In conclusion, carbamazepine remains a pivotal treatment option for focal seizures, yet the singular reliance on testing for the HLA-B*1502 allele may prove inadequate in preventing severe cutaneous adverse reactions such as Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) within the Asian population.

While the presence of the HLA-B*1502 allele is a well-established risk factor for carbamazepine-

induced SJS/TEN, individuals lacking this genetic marker can still experience these reactions. Therefore, having HLA-B*1502 that increased the risk , but having HLA-B*1502 does not mean protective against carbamazepine-induced SJS/TEN; rather, it suggests a different genetic susceptibility profile or potential involvement of alternative mechanisms in the development of these reactions. Given the potential overlap with erythema multiforme (EM), vigilance in monitoring disease progression, removal of causal factors and prompt initiation of therapeutic interventions are imperative to mitigate further complications. This case underscores the importance of heightened awareness among pediatricians and general physicians regarding the possibility of SJS/TEN manifestation in patients lacking the HLA-B*1502 allele, thereby facilitating more effective management strategies and ensuring optimal patient care.

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REFERENCES

1. Liotti, L., Caimmi, S., Bottau, P., Bernardini, R., Cardinale, F., Saretta, F., Mori, F., Crisafulli, G., Franceschini, F., & Caffarelli, C. (2019, January 29). Clinical features, outcomes and treatment in children with drug induced Stevens-Johnson syndrome and toxic epidermal necrolysis. Acta bio-medica: Atenei Parmensis. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6502171/. doi: 10.12688/f1000research.20419.1
2. Ferrell, P. B., & McLeod, H. L. (2008, October). Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. Pharmacogenomics. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2586963/#:~:text=The%20HLA%2DB*1502%20allele%20is%20highly%20associated%20with%20the,syndrome%20and%20toxic%20epidermal%20necrolysis. doi: https://doi.org/10.2217%2F14622416.9.10.1543
3. Krauss, G. (2006). Current understanding of delayed anticonvulsant hypersensitivity reactions. Epilepsy Currents. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1408282/. doi: 10.1111/j.1535-7511.2006.00089.x
4. Tangamornsuksan W, Chaiyakunapruk N, Somkrua R, Lohitnavy M, Tassaneeyakul W. (2013, September). Relationship between the HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. JAMA Dermatology, 149(9), 1025-1032. doi: 10.1001/jamadermatol.2013.4114. [PubMed: 23884208]
5. Capule F, Tragulpiankit P, Mahasirimongkol S, Jittikoon J, Wichukchinda N, Theresa Alentajan-Aleta L, James Barit JV, Casanova-Gutierrez J, Cabral-Lim L, Baltazar Reyes JP, Roa F, Salonga R, San Gabriel KF, Lynn Silao C. Association of carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis with the HLA-B75 serotype or HLA-B*15:21 allele in Filipino patients. Pharmacogenomics J. 2020 Jun;20(3):533-541. doi: 10.1038/s41397-019-0143-8.