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Mini Review

Cutaneous Adverse Drug Reactions to Antiepileptic Drugs

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Abstract

Discontinuation of Antiepileptic Drugs (AEDs), primarily prompted by adverse effects, presents a formidable challenge in the management of epilepsy, impacting up to 25% of patients. This article thoroughly explores the clinical spectrum of Cutaneous Adverse Drug Reactions (cADRs) associated with commonly prescribed AEDs. Ranging from mild maculopapular rashes to life-threatening conditions such as Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), the diverse manifestations are meticulously detailed. Diagnostic strategies, incorporating red flags and testing methodologies, are elucidated to ensure precise identification.

The classification of Adverse Drug Reactions (ADRs), with a specific focus on cADRs and their association with type A or type B reactions, is presented. Critical risk factors, encompassing patient demographics, drug-related skin reactions, and genetic predispositions, are thoroughly explored. The article underscores the role of Human Leukocyte Antigens (HLAs), including HLA*15:02, in predicting susceptibility to severe reactions like SJS/TEN, particularly with aromatic AEDs prevalent in specific populations.

Management strategies for varying cADR severities are discussed, placing emphasis on drug discontinuation, symptomatic relief, and potential desensitization. The article concludes by consolidating current knowledge, providing clinicians with a roadmap for navigating the complexities of diagnosis and management. The integration of personalized medicine principles and evidence-based approaches emerges as a crucial paradigm for the future of epilepsy management, aiming to minimize the impact of ADRs on patient outcomes.

ABBREVIATIONS

ADR: Adverse Drug Reaction; AED: Antiepileptic Drug; AGEP: Acute Generalized Exanthematous Pustulosis; ATP: Atopy Patch Test; BSA: Body Surface Area; cARD: Cutaneous Adverse Drug Reaction; CBZ: Carbamazepine; DRESS: Drug Reaction With Eosinophilia And Systemic Symptoms; GBFDE: Generalized Bullous Fixed Drug Eruption; HLA: Human Leukocyte Antigen; LTG: Lamotrigine; PB: Phenobarbital; PHT: Phenytoin; OXC: Oxcarbazepine; SJS: Stevens-Johnson Syndrome;TEN: Toxic Epidermal Necrolysis; SCAR: Severe Cutaneous Adverse Reaction

INTRODUCTION

Adverse reactions significantly impede epilepsy management, leading to treatment discontinuation in approximately one-quarter of patients, thereby obstructing the attainment of efficacious therapeutic dosages. Moreover, these reactions substantially contribute to increased disability, morbidity, and mortality, exerting a considerable burden on healthcare resources and expenditures [1].

Notwithstanding the effectiveness of routinely prescribed Antiepileptic Drugs (AEDs) like carbamazepine, phenytoin, lamotrigine, oxcarbazepine, and phenobarbital in seizure mitigation, their utilization is frequently hindered by the prevalent occurrence of Adverse Drug Reactions (ADRs) [2].

Cutaneous Adverse Drug Reactions (cADRs) to AEDs are notably prevalent, with an in-patient incidence rate of around 3%. Arif, et al.'s study observed a 15.9% incidence of rash in 1649 AED-treated patients over five years. These ADRs often manifest as idiosyncratic responses, not correlating with dosages. Despite their relatively low frequency, the most severe idiosyncratic cADRs, like Stevens-Johnson syndrome and toxic epidermal necrolysis, pose significant risks of mortality or severe disability [3,4].

Recent advancements in epidemiological understanding and pharmacogenetics have enhanced our comprehension of AED-related toxicities. This progress facilitates the identification of patient subgroups at an elevated risk for specific adverse reactions, allowing preemptive testing for certain genetic mutations to avert severe ADRs [1].

This review aims to elucidate the clinical presentations of various cADRs and discuss the identification of patients at risk for severe reactions. It also provides an overview of the primary AEDs causing these reactions and examines genetic mutations predisposing patients to these adverse effects.

Classification of Adverse Drug Reactions

Adverse Drug Reactions (ADRs) are systematically classified into distinct categories. The World Health Organization delineates five primary types: Type A, acute pharmacological reactions; Type B, idiosyncratic responses; Type C, chronic reactions; Type D, delayed responses; and Type E, those secondary to drug-drug interactions. Additionally, these reactions are stratified by hypersensitivity timelines into immediate (Type I) and delayed (Type IV) hypersensitivities [1,2].

Focusing on Antiepileptic Drugs (AEDs), adverse effects are typically categorized into cognitive and coordination impairments; mood and emotional disturbances; sleep-related issues; integumentary and mucosal disorders; and alterations in weight and cephalalgia. This review centers on cutaneous ADRs (cADRs), frequently falling within Type A or Type B classifications, and are commonly concomitant with Type IV hypersensitivity reactions [1].

Risk Factors

Pertinent risk determinants for Cutaneous Adverse Drug Reactions (cADRs) include extremes of age, as seen in pediatric and geriatric demographics, antecedent drug-elicited dermal reactions, escalated initial drug dosages, and rapid titration protocols. Moreover, immunological disorders such as HIV, hepatic pathologies, and specific concomitant pharmacotherapies augment the susceptibility. Pertinently, in the Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, infectious etiologies may contribute to its pathogenesis, with human herpesvirus [5-7], alongside Epstein-Barr virus, implicated as potential etiological agents [2].

Genetic predisposition plays an instrumental role in the hypersensitivity to Antiepileptic Drugs (AEDs), with specific Human Leukocyte Antigens (HLAs) robustly associated with an enhanced risk of cADRs to AEDs. Notably, HLA*15:02 is recognized as a considerable risk factor for the occurrence of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) subsequent to carbamazepine administration, boasting high sensitivity and specificity rates. Such findings are suggested to extend to other AEDs, including phenytoin, lamotrigine, and oxcarbazepine. Pre-prescriptive screening for these alleles is advocated in regions with a high prevalence, thereby mitigating the risk of severe cADRs. Additional predisposing genetic markers are delineated in Table 1.

CLINICAL PRESENTATION

Cutaneous Adverse Drug Reactions (cADRs) represent prevalent Type B adverse effects linked to Antiepileptic Drug (AED) utilization. Within a Japanese study cohort, such reactions accounted for three-quarters of all AED-related ADRs [8,9]. The clinical spectrum of cADRs is heterogeneous, extending from mild maculopapular eruptions to life-threatening entities such as Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome. This diversity encompasses urticaria, pruritus, alopecia, and erythema multiforme [2].

Maculopapular eruptions, characterized by erythematous and pruritic macules and papules, emerge typically within seven to fourteen days post-AED initiation, subsiding spontaneously subsequent to the cessation of the causative agent. Prevalence rates of such rashes span from 5-17% among patients administered carbamazepine, phenobarbital, phenytoin, and lamotrigine [1].

Urticarial reactions, predominantly observed in pediatric and young adult cohorts, particularly those with a history of atopy, manifest as transient, itchy wheals [10].

Fixed drug eruptions, presenting as solitary or multiple erythematous or violaceous patches or bullae, emerge within a week of drug exposure, with recurrence at identical sites upon rechallenge. This condition may progress to a generalized bullous fixed drug eruption, posing a therapeutic challenge due to its extensive body surface involvement, mimicking SJS/TEN [11].

Acute Generalized Exanthematous Pustulosis, a rare manifestation, is characterized by fever, pustular lesions primarily on the trunk, and leukocytosis, occurring at an incidence of 0.1-0.5 per 100,000 in the population [10].

Table 1: HLA alleles associated with high risk of ADRs due to AEDs.

HLA	High-Prevalence Population	Cutaneous Manifestations	Drugs Associated with Higher Risk
HLA-B*15:02	Hong Kong, Malaysia, Thailand, Philippines, Han Chinese	SJS/TEN	CBZ, PHT, LTG, OXC.
HLA-31*01	Japan, South India, Native Americans, Europe, South Korea, Han Chinese	SJS/TEN,DRESS syndrome, maculopapular eruptions	CBZ
HLA-A*24:02	South China	SJS/TEN	Aromatic AEDs
HLA-B*1511	Japan, Korea, Central China	SJS/TEN	CBZ
HLA-A*02:01/ Cw*15:02	Caucasians	SJS/TEN	PHT
HLA-B*1301,HLA-B*5602, HLA-B*5604	Thailand	DRESS syndrome, drug hypersensitivity syndrome	PHT

HLA: Human Leukocyte Antigens, **ADR**: Adverse Drug Reaction, **AED**: Antiepileptic Drug, **SJS/TEN**: Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis, **CBZ**: Carbamazepine, **PHT**: Phenytoin, **LTG**: Lamotrigine, **OXC**: Oxcarbazepine, **DRESS**: Drug Reaction with Eosinophilia and Systemic Symptoms [5-8].

SJS and TEN, both severe and potentially fatal cADRs, are marked by extensive epidermal necrolysis. SJS is diagnosed with less than 10% body surface area involvement, whereas TEN involves greater than 30% [12-14].

DRESS syndrome is also life-threatening but exhibits a varied clinical presentation. Skin lesions are polymorphic and non-specific, while systemic involvement is prominent, including fever, leukocytosis with eosinophilia or atypical lymphocytosis, lymph node enlargement, and liver or renal dysfunctions developing two to six weeks after drug exposure [15]. In a systematic review evaluating DRESS syndrome in the pediatric population, AEDs were the culprit drugs in 97% of cases (n=148), with CBZ accounting for 34%, PHT 30%, LTG 16%, PB 10%, OXC 3%, valproic acid (VPA), and levetiracetam (LEV) 1% each [14].

Incidences of severe mucocutaneous reactions such as DRESS and SJS/TEN range from 1-10 per 10,000 new AED users, with AEDs implicated in over half of DRESS cases. Carbamazepine is frequently associated with both DRESS and SJS/TEN, alongside more benign reactions such as erythematous rashes and alopecia [1,15,16].

DIAGNOSIS

In patients manifesting cutaneous eruptions subsequent to Antiepileptic Drug (AED) initiation, a meticulous dermatological evaluation is imperative. Clinicians must remain vigilant for sentinel signs suggestive of serious dermatologic conditions, such as Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), or Acute Generalized Exanthematous Pustulosis (AGEP). These indicators include but are not limited to fever, angioedema, lymphadenopathy, hemorrhagic dermatitis, Nikolsky's sign, mucosal ulceration, systemic symptoms (e.g., cardiac arrhythmia, arterial hypotension, lethargy, cachexia), erythroderma, dermal hypersensitivity, and cervical or truncal erythema, accompanied by laboratory anomalies [17].

Ascertainment of the offending AED typically entails provocative testing, yet this is contraindicated in the setting of severe cutaneous adverse reactions (SCARs) due to inherent risks. The Atopy Patch Test (APT) offers a safer modality, applying a nominal drug dose cutaneously with subsequent evaluation for hypersensitivity reactions. Delayed intradermal testing, akin to APT, is deferred until cutaneous manifestations have fully resolved [10].

MANAGEMENT

The management of Adverse Drug Reactions (ADRs) necessitates a nuanced approach, tailored to the clinical manifestations and the severity of the reaction. Universally, cessation of the offending agent is a critical first step.

For benign dermatoses, such as fixed drug or maculopapular eruptions, the recommended strategy includes symptomatic alleviation. Dermatologic discomfort may be mitigated with potent topical glucocorticoids or systemic H1 antihistamines. Concurrent mild oral lesions may be addressed with topically applied corticosteroids or calcium carbonate preparations. Absent warning signs, a judicious reduction in AED dosage with vigilant patient observation is warranted, advancing to gradual titration upon clinical improvement. Established hypersensitivity necessitates substitution of the AED; careful consideration is required when replacing with another aromatic AED due to cross-reactivity risks. In scenarios of mild hypersensitivity, desensitization protocols may be considered, subject to informed patient consent and close monitoring [10,11].

In cases suggestive of a Severe Cutaneous Adverse Reaction (SCAR), the creation of an exhaustive pharmacological history is indispensable to discern the temporal relationship between drug exposure and symptom onset. Prompt withdrawal of non-essential pharmaceuticals, inclusive of the presumptive agent, is pivotal and prognostically advantageous. Rechallenge is contraindicated under such circumstances [18-20].

In instances of Acute Generalized Exanthematous Pustulosis (AGEP), management is conservative, emphasizing symptomatic relief through topical corticosteroids, skin hydration, and infection prophylaxis. AGEP typically resolves without sequelae [17].

Generalized Bullous Fixed Drug Eruption (GBFDE) warrants an approach paralleling that of AGEP, with the potential inclusion of systemic corticosteroids, despite a lack of robust evidence for their efficacy [11].

SJS/TEN patients necessitate hospital-based care. Utilization of the ALDEN algorithm can aid in identifying the causative medication. BSA involvement is integral for distinguishing SJS from TEN and appraising disease gravity. Multidisciplinary management encompasses supportive measures, meticulous skin care, thermoregulation, nutrition, analgesia, infection control, and complication management. Pharmacological intervention remains uncertain; however, systemic corticosteroids, intravenous immunoglobulin, cyclosporine, plasmapheresis, or anti-TNF agents may be contemplated [19].

For DRESS syndrome, drug withdrawal is paramount. Systemic corticosteroids remain the cornerstone of pharmacotherapy, supplemented by evolving evidence for cyclosporine as a steroid-sparing agent. The role of antiviral agents is considered in the context of potential viral reactivation. Mortality rates approximate 5-10% [20,21].

CONCLUSION

The management of epilepsy is confronted with significant challenges attributed to the prevalence of adverse effects. While some cutaneous reactions may present as mild and self-limiting, others can lead to a decline in quality of life, disability, and, in severe cases, mortality. A comprehensive understanding of the diverse range of reactions is imperative for precise diagnosis and tailored management. The identification of risk factors, spanning from patient demographics to genetic predispositions,

offers valuable insights for anticipating and preventing adverse reactions. It is noteworthy that aromatic Antiepileptic Drugs (AEDs) are the most frequently implicated culprits.

The outlined treatment strategies underscore the necessity for personalized approaches based on the severity of Adverse Drug Reactions (ADRs). Whether addressing mild reactions or tackling severe conditions such as Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis (SJS/TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, discontinuation of the implicated drug stands as a fundamental step. Symptomatic management, dosage adjustments, and desensitization techniques are tailored to the specific clinical presentation and the patient's individual profile.

In summary, this review consolidates the current knowledge surrounding cutaneous adverse effects linked to AEDs, offering a roadmap for clinicians to navigate the intricate landscape of diagnosis and management. The integration of principles from personalized medicine and the incorporation of evolving evidence-based approaches will undeniably shape the future of epilepsy management, mitigating the impact of ADRs on patient outcomes.

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