Delayed hypersensitivity to antiepileptic drugs in children

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Abstract

Background: Antiepileptic drugs (AEDs) are widely used for the treatment of epilepsy, but they can be associated with the development of mainly delayed/non-immediate hypersensitivity reactions (HRs). Although these reactions are usually cutaneous, self-limited and spontaneously resolve within days after drug discontinuation, sometime HRs reactions to AEDs can be severe and life threatening.

Aim: This paper seeks to show examples on practical management of AEDs HRs in children starting from a review of what it is already known in literature.

Results: Risk factors include age, history of previous AEDs reactions, viral infections, concomitant medications and genetic factors. The diagnosis work-up consists of in vivo (Intradermal testing and Patch testing) and in vitro tests [serological investigation to exclude the role of viral infection, lymphocyte transformation test (LTT), cytokine detection in ELISpot assays and granulysin (Grl) in flow cytometry]. Treatment is based on a prompt drug discontinuation and mainly on the use of glucocorticoids.

Conclusion: Dealing with AEDs HRs is challenging. The primary goal in the diagnosis and management of HRs to AEDs should be trying to accurately identify the causal trigger and simultaneously identify a safe and effective alternate anticonvulsant. There is therefore an ongoing need to improve our knowledge of HS reactions due to AED medications and in particular to improve our diagnostic capabilities.

Introduction

Antiepileptic drugs (AEDs) are widely used for the treatment of epilepsy, a condition which affects approximately 10 million children globally(1-3). According to their chemical structure, AEDs are classified as aromatic if they have at least one aromatic ring [lamotrigine (LTG), carbamazepine (CBZ), phenobarbital (PHB), phenytoin (PHT), oxcarbazepine (OXC), felbamate, zonisamide, primidone]or nonaromatic [sodium valproate (VPA), topiramate, levetiracetam (LEV), clobazam, ethosuximide, gabapentin, pregabalin, vigabatrin and lacosamide](1-3). Hypersensitivity reactions (HRs) to AEDs are mainly cutaneous and occur in 3% to 16% of children receiving anticonvulsants (4). The most common cutaneous reactions are generalized maculopapular exanthema (MPE) and delayed urticaria(1,5). These reactions are non-immediate (delayed type from 1 hour after the initial drug administration, commonly after many days of treatment) in onset and thought to be predominantly T-cell mediated. Although these reactions are usually self-limited and spontaneously resolve within days after drug discontinuation, reactions can be severe and life threatening. These reactions often occur during dose escalation, from the second to the eighth week of initiation of

therapy. A high starting dose or co-administration with other AEDs are additional risk factors(6). AEDs, in particular aromatic compounds (such as PHT, CBZ, OXC, PHB and LTG) (7), are among the most frequent causes of life-threatening severe cutaneous adverse reactions (SCARs), which consist of Steven-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and, very rarely, acute generalized exanthematous pustulosis (AGEP)(1-3, 5,8-11). Large pediatric series revealed that AEDs were the most frequently incriminated drug group associated with DRESS and SJS/TEN (12-17). Although most cases were related to aromatic AEDs, including LTG, rare reports of SJS/TEN related to new generation AEDs such as LEV have been published (14-19). Recently, there have been an increased number of reports of LEV induced HRs, including severe reactions such as DRESS, SJS/TEN, AGEP and cytopenia among children and adults(20).

A recent nationwide registry-based population study in Korea showed that VPA and LEV were the significant emerging AEDs causing SCARs in addition to the well-known offending AEDs such as CBZ and LTG. Finally, aplastic anemia, drug-induced liver injury (DILI) and pancreatitis are rare but severe HRs reported in adult and pediatric patients receiving AEDs, especially VPA and those that are aromatic(2, 10,21,22). So far geographical variation in incidence of severe reactions, and association with certain HLA alleles are well described and even more studied in the literature.

This paper seeks to show examples on practical management of AEDs HRs in children starting from a review of what it is already known in literature (see graphical abstract). At the hospital admission and according to the hospital ethic committee form, all children's parents signed an informed consent to the processing of clinical data for future research studies.

Immune pathomechanisms, Risk factors and Genetics

AEDs can bind directly to human leukocyte antigen (HLA) or T-cell receptor (TCR), according to pharmacological interaction (p-i concept)(23).

In addition to the chemical structure of the drug (aromatic rings), risk factors which are important for the development of HRs to AEDs include age and gender, history of previous AEDs reactions, viral infections, concomitant medications and genetic factors (1,2, 24). Age-related differences in drug metabolism (the reduction in glucuronide conjugation in infants, faster rate of CYP-mediated reactions in infants and children) may result in an increase in hypersensitivity to AEDs in young children(5, 25-28). Children younger than 5 years of age have up to 5 times higher risks for development of SCARs and rashes induced by AEDs (2, 21, 29). In general, HRs to AEDs are more frequent among children who are younger than 12 years, as well as those who use aromatic or multiple AEDs (1,5). A recent prospective study examined HRs to AEDs during childhood and revealed that the rate of CBZ-associated DRESS was remarkably higher in children than in adults. In addition, children who used a single AED had a lower frequency of HRs than those who used multiple AEDs; 3.8% *vs* 4.4%, respectively (5). Moreover, the overall incidence rate of SJS/TEN among children was reported to be 5 to 7 cases per million person-years which is higher than adults in some nationwide studies(30-34). Despite an increased frequency of HRs to AEDs in childhood, recent studies showed that the risk of death with SJS/TEN is lower in children than in adults (14,30,32,34).

Given the above knowledge, the concomitant administration of AEDs should always be undertaken with caution and using a slower titration (14,27,35,36). For example, among AEDs, VPA has been accepted to be among the safest medications(13-15). However, even at low concentrations, VPA is known to decrease LTG clearance leading to higher serum concentrations of the latter, which in turn increases the risk of severe reactions, an important risk factor for severe reactions(6).

An additional cofactor in AED-induced DRESS is viral infection. It remains controversial as to whether the herpes viral infection or reactivation of the latent viral genome is a triggering cofactor, or a result of HR to the drug itself (1,2).

A few pediatric studies showed the significant associations between certain HLA alleles and AED-induced HRs such as: in Thai children (37) HLA-A*01:01 and HLA-B*13:01 and PHB

hypersensitivity, in Singapore children of Chinese and Malay ethnicity (38) HLA-B*15:02 and CBZ-induced SCAR and in children from North America with a diverse ethnic background (39) HLA-A*31:01 and CBZ-induced DRESS and MPE as well as HLA-B*15:02 and CBZ-induced SJS. Also, the association between *HLA-A*31:01* and CBZ-induced SCAR and MPE has been confirmed across populations in Europe and in the Far East(37,40).

Specifically, several genome-wide association study investigations from Han Chinese (Taiwan) (41), European (40, 41), Canadian (mixed ethnicity) (39), Spanish Romani (42) and Korean (43) confirmed a strong HLA A* 31:01 association with CBZ-induced DRESS and/or MPE, but not for SJS/TEN.

A very strong association between HLA-B*15:02 and CBZ-induced SJS/TEN has been proven in the Han Chinese and Southeast Asian populations, including children (38,44), with a recommendation by US FDA that all patients within these ethnic groups should be genotyped for HLA-B*15:02 before commencing CBZ treatment (45). In the Han Chinese population, HLA-A*24:02 was also significantly associated with SJS induced by the aromatic AEDs as a whole group(46).

However, a pediatric multicenter multiethnic consortium study in Canada showed that HLA-B*15:02, but not HLA-A* 31:01, was associated with SJS related to CBZ (39). A recent International study identified that HLA-B*57:01 was found as a new genetic risk factor for susceptibility to CBZ-induced SJS/TEN in Europeans (47). Genetic alterations in drug metabolism may also play an important role in SJS/TEN and other severe HRs to AEDs (48-51). Moreover, an association between a rare variant in the complement factor H-related 4 (*CFHR4*) gene and PHT-induced MPE in Europeans has been also recently reported (52).

The presence of common allergies was not found to be a significant risk factor for AEDs cutaneous reactions(53).

Diagnosis

The identification of the culprit drug can be a clinical challenge as patients are frequently on multiple AED treatment regimens at the time of presentation and the clinical spectrum of symptoms and signs varies enormously. The diagnosis aims to identify the trigger medication and in so doing prevent re-exposure, whilst simultaneously identifying safe age and disease-appropriate alternative AED. Diagnostic steps include a detailed clinical and medication history as well as physical examination (this may be facilitated by clinical images that have been recorded). Additional investigations may include skin testing, in vitro tests and/or drug provocation test (DPT) (1, 2, 5,9). Diagnostic criteria and drug causality assessment scores have been developed for use in the acute phase of severe reactions such as DRESS or SJS/TEN (54-59).

Laboratory tests and serological investigation to exclude the role of viral infection as co-factor should also be undertaken. The identification of the culprit AED may be also be made on patch tests (PTs), delayed reading of intradermal test (IDTs) or in-vitro tests. In selected patients, drug provocation test (DPT) may be undertaken based on risk profile. Standardized protocols of DPTs with AEDs are lacking. Considering that almost all AED HRs are nonimmediate, one-tenth of the maximum single unit dose could be administered, and in case of tolerance a full dose can be administered 1 to 7 days after, depending on the time interval of the index reaction. If the benefit of treatment outweighs potential risks, the one-tenth dose (if tolerated) could be followed one hour later by a full dose and if it is tolerated, a normal course of the drug can be administered.

Anyway, DPTs are contraindicated in SCARs due to the risk of inducing severe reactions(1,5). As DPTs are seldom performed even when skin tests are negative, it is difficult to validate the diagnostic performance of PTs, IDTs and in vitro tests.

Skin testing (patch and intradermal tests)

PTs and IDTs may be undertaken in patients presenting with a benign rash, a low clinical suspicion or in order to exclude cross reactivity, which is highly prevalent (40-80%) among aromatic AEDs (1,4,5,9,60-64).

In delayed reactions such as MPE and SCARs, the allergy work-up may include skin testing with PTs first and then delayed reading of IDTs (PTs are considered safer than IDTs). It has been recommended to perform skin testing and PTs at least 4 weeks after the disappearance of the cutaneous reaction and discontinuation of systemic glucocorticoids or immunosuppressants, as well as, in the case of PTs, 4 weeks after any exposure to ultraviolet rays of the skin area to be tested and one week after discontinuation of topical glucocorticoids on the test site. In DRESS, PTs must be performed at least 6 months after the disappearance of the cutaneous reaction and after verification by quantitative real-time polymerase chain reaction on plasma of the absence of reactivation of viruses of the herpes group. For IDTs, sterile injectable solutions are obligatory. However, few AEDs are available in these formulations (e.g., PHB, PHT, VPA, LEV and lacosamide). Reading of delayed reactions to skin tests are performed after 48 and 72 hours. For IDTs, any infiltrated erythema with diameter larger than 5 mm is considered to be a positive reaction. Patch test diagnostic criteria are identical to those used for contact allergy: -(no reaction), +/- (doubtful reaction, faint erythema only), + (erythema, infiltration, possibly discrete papules), ++ (erythema, infiltration, papules and vesicles), and +++ (intense erythema, infiltration and coalescing vesicles).

IDTs are not generally recommended in SJS/TEN, due to the unproven risk of inducing a reaction(2,65-67).The safety of IDTs in DRESS is currently unknown and may be undertaken in select cases using diluted drug concentrations if PTs are negative and increasing concentrations by a minimum of one weak interval.

The maximum non-irritant and optimal diagnostic concentrations for IDTs with AEDs are not well defined (1, 2) but there is published data suggesting the maximum recommended concentrations for PTs to be 10% in petrolatum (pet) for pure substances, and 30 % (20 % for CBZ) in pet for

206commercialized forms of AEDs (66,68,69). It is recommended to start at a concentration of at least
2071% and, if negative, to gradually increase the concentration for severe cases (60, 69,70).
208PTs positivity has most commonly been reported in patients presenting with either DRESS or MPE.
209The diagnostic value of PTs has been studied mainly for CBZ and the rate of positive PTs has been
210reported in the range of 19.7% to 100% (5, 70-76). The diagnostic value of PTs in DRESS varies
211according to the incriminated drug, with a reported higher sensitivity for CBZ, compared with PHT
212and PHB (9,66,71,72). Of note, it has been suggested that patch testing with the incriminated drug
213as well as with its metabolites could increase the diagnostic value (70, 73). However, these data
214need to be confirmed by further studies, particularly in the pediatric population. In organ-specific
215reactions, such as agranulocytosis and DILI, skin tests have no value and DPT is contraindicated(2,
21665). As always in drug allergy, only positive skin tests are taken into account (proving
217sensitization), negative skin tests do not eliminate the responsibility of the drug.

218**In vitro testing**

219Regarding in vitro tests, lymphocyte transformation test (LTT), cytokine detection in ELISpot
220assays and granulysin (Grl) in flow cytometry have been studied for delayed T-cell mediated drug-
221induced reactions (9,65, 77-81).A systematic review of the role of in vitro methods for diagnosis of
222SCARs induced mostly by aromatic AEDs was recently published (81). The LTT can be useful and
223up to 60% of the patients with nonimmediate cutaneous reactions (i.e. MPEs) have positive results
224particularly in the case of CBZ and PHT HRs (82).The LTT should be ideally performed 6 to 8
225weeks after the initial reaction to minimize the effects of a possible refractory period immediately
226after the reaction as well as the potential decrease of sensitivity over time (9,66,82,83).Anyway,
227controversy exists regarding the optimal phase of the reaction to perform LTT: for SJS/TEN, higher
228sensitivity has been found in the acute phase and for DRESS in the resolution phase, 5-8 weeks
229after the onset of skin rashes (82), while other studies found no differences.

The performance of LTT is poorly studied in children(71,77,83).In a pediatric population with a control group, the LTT had a sensitivity and specificity of 58.4% and 95.8%, respectively. In particular, 3 out of 4 children with severe reactions to CBZ had a positive LTT. All the control patients were negative. Similarly, in a pediatric study of 7 children with DRESS to CBZ, all returned positive LTTs to CBZ; PTs were positive in 6 of the 7 patients (83,84).The positive and negative predictive value of LTT generated from this study of low numbers was therefore 93.3 and 69.9% (84).Data on cross-reactivity are scarce especially in children. In general, LTT sensitivity reported in severe bullous diseases is 25% to 75% (85,86).In particular, the sensitivities and specificities of different in vitro methods in SJS/TEN ranged between 37% to 86% and 86% to 100%, respectively (80). Some studies found that the combination of different methods increased both the sensitivity and specificity of isolated methods (79,87). A recent paper found a good correlation between LTT results and ALDEN score among SJS/TEN cases(88). Limitations of LTT include the use of radioactive material (banned in most hospitals nowadays), the technical skills linked to it and therefore its availability everywhere and cost. In the absence of confirmatory DPTs the true diagnostic value of skin tests and in vitro tests in SJS/TEN remains unknown.

Management and treatment

The first and most important step in the management is the identification and avoidance of the causative drug. Early discontinuation of the suspected drug is associated with a better clinical outcome and most reactions subside within a few days. There is no published experience of "treating through" as for other drugs.

During the acute phase of AEDs HRs(especially in DRESS),the avoidance of new AED drugs, when possible, is important as neo-sensitization(new-onset allergy caused by sensitization to cross-reacting allergens)has been described(54,55,89).

Additional steps in the management of the acute reaction differ depending on the type of SCARs. The value of glucocorticoids and antihistamines in the management of MPEs remains controversial, but they are frequently used (90).

Consensus document or guidelines detailing the management of DRESS reactions are lacking with the consequence that management is based on clinical cases and expert opinion(89). In mild forms, treatment is mainly supportive and symptomatic. In moderate cases without visceral involvement, glucocorticoids are usually adequate (91). Systemic steroid therapy is advised to treat cases of moderate to severe disease. Several aspects (i.e. optimal dose, route of administration, duration of treatment, and rapidity of dose tapering) of steroid treatment have not been rigorously assessed (92).The rapid tapering of steroid therapies has been associated with relapse of DRESS (92, 93).Tapering should therefore best be undertaken over a three to six months period. Mepolizumab (anti IL-5) and cyclosporine have been proposed as second-line therapies in adults for DRESS treatment (94,95). Other potent immunosuppressant medications used in the treatment of severe DRESS/ cortico-resistant cases are azathioprine, rituximab, infliximab, and mycophenolate, sometimes in association with intravenous immunoglobulins (IVIG) and plasmapheresis (96-99). IVIG have been reported to be useful in a few adults with DRESS and detrimental in others (100). Due to the fact that there is a major herpes viral reactivation along with presence of life-threatening signs, it has been proposed to administer anti-viral medications (e.g. ganciclovir) in combination with steroids with or without IVIG, but the efficacy is unclear (101).

The management of SJS/TEN in the acute phase should be multidisciplinary and includes symptomatic and supportive treatments, dermatologic care, targeted therapies such as systemic glucocorticoids, IVIG and cyclosporine, and mechanistic therapies (2, 88, 89, 102-103). A specific severity-of-illness model has been developed (Score of Toxic Epidermal Necrolysis -SCORTEN) and is the most frequently used scoring system to predict the prognosis of SJS/TEN and calculate the probability of mortality(104).

With the identification and avoidance of the trigger AED in place, a decision – in association with the primary treating clinician, patient and family- will rapidly need to be made with respect to the need for and selection of alternate AEDs. In patients with previous reactions to an aromatic AED, other aromatic AEDs should be avoided as there is a high degree of cross-reactivity. Benzodiazepines, LEV, topiramate and VPA would be more favourable alternate AEDs as lower allergenic potential has been reported (105).

In mild delayed reactions when there are no valid alternatives, the advantages of a desensitization protocol should be evaluated since only few case reports are available (106-107). Whilst desensitization is generally restricted to IgE-mediated allergic reactions, there may be a role for slow incremental exposure (over days to weeks) depending on the clinical need for a particular AED in the setting of a mild reaction. Protocols on desensitization in these kinds of delayed reactions in pediatric populations are not standardized. Desensitization is contraindicated in SCARS (especially in DRESS and SJS) (108).

We present three teaching case reports of HRs to AEDs in children, in which we describe practical management, treatment and allergy investigations performed during follow up visits in three different clinical scenarios: MPE, DRESS and SJS/TEN.

MPE to AEDs - ***Clinical Case***

A 10-year-old boy was diagnosed with a Rubinstein-taybi syndrome and epilepsy (partial seizures, and absence seizures)6 months prior to presentation, and was started on LEV due to seizures three weeks before. There was a good clinical response but on the second week of LEV treatment he contacted the neurology department due to facial erythema, and a MPE of the upper part of thorax and arms with mild pruritus(Figure 1). He had no fever. His physical examination was otherwise normal for the patient and no lymphadenopathy was observed. Peripheral blood evaluation showed a slightly elevated white blood cell (WBC) count of 12.200/μL with no atypical lymphocytes and normal eosinophils count. C-reactive protein level was within normal, as was the aspartate

aminotransferase (AST) level, alanine aminotransferase (ALT) level and creatinin level. LEV was discontinued but the rash spread to the abdomen and he had scattered lesions on the limbs over the next two days. Hence, he was prescribed oral antihistamines and systemic prednisolone (1 mg⁄kg⁄day). On day five, the rash subsided and the patient started treatment with VPA. Complete cutaneous resolution was noticed on day eight. The patient was referred to the allergy department and evaluated two months after the suspected reaction. Skin patch test with LEV in 30% pet was grade 2 positive and VPA was negative. There was no recurrence of seizure nor rash on follow-up.

DRESS to AEDs - ***Clinical Case***

An 11-year-old girlwas admitted to the emergency room with complaints of a sudden-onset itchy maculopapular rash and fever of 38.5°C. The rash initially involved just her hands butthen spread all over her face, torso and extremities. CBZ as antiepileptic treatment had been commenced three weeks earlier (Figure 2). Physical examination revealed normal vital signs and no lymphadenopathy nor hepatosplenomegaly. The blood exams showed high level of eosinophils (WBC 4250 cell/mcl with 11% atypical lymphocytes; EOS percentage:18.5%; absolute number: 786.25), and high level of ALT (510 UI/L). Serological studies for concomitant infective agents [Epstein Barr virus (EBV), Mycoplasma pneumoniae, human herpes virus (HHV)-6, Streptococcus pneumoniae] were negative. Given that, the average latency period for CBZ is between two to sixweeks, CBZ was clinically suspected as the causative trigger. Based on her RegiSCAR score of 4 (Table 1), an acute MPE, fever (greater than 38° C), eosinophilia (greater than 700 cells/μL), involvement of one organ, transiently disturbed liver function tests and negative serological studies for concomitant infective agents, a diagnosis of ‘probable’ DRESS was made. According to the diagnostic criteria for DRESS established by the Japanese consensus group, the patient fulfilled five of the seven criteria, establishing the diagnosis of atypical DRESS(Table 2).

A skin biopsy was not performed. The patient was advised to stop CBZ and was treated with oral glucocorticoids (prednisone, 1 mg/kg/day for twoweeks) and antihistamines (cetirizine 10 mg one a day for two weeks) with recovery after two weeks.

After three months the patient was referred to the Allergy Unit for a complete allergy work up. She underwent PTs with 20% CBZ in petrolatum with a positive reading at 48 hours(Figure 3). PT to cross-reactive AEDs were suggested in order to complete allergy investigations, but parents refused.

After 3 months from stopping CS treatment LTT was performed and resulted positive.

SJS and TEN to AEDs - *Clinical case*

A 4-year-old Caucasian girl was admitted to pediatric wards for the assessment of fever (present for five days), malaise and sore throat. She was prescribed amoxicillin(AMOX) for upper respiratory infection. The following day oral ulcers and a painful erythematous macular rash on the trunk and extremities appeared, some of which started evolving into blistering. She had normal vital signs except for an ongoing fever of 38.7^{o}C and tachycardia. Cutaneous examination revealed widespread flat violaceous macules showing two concentric zones, some of which were confluent, or with bullae, in addition to extensive erosive oral mucositis and conjunctivitis(Figure 4). Laboratory tests revealed increased acute phase reactants and increased serum AST and neutrophilia. The mucosal lesions extended to lower pharynx and proximal esophagus with severe dysphagia. About 25% of total body surface area showed epidermal detachment with a positive Nikolsky's sign. A skin biopsy from the skin lesion was taken. Her relevant medical history included mild cerebral palsy secondary to hypoxic ischemic syndrome at birth. VPA had been taken for seizure control for years. Three weeks prior to admission, a new aromatic AED, LTG, was added to her treatment regimen and had been tolerated. There was no known family history of blistering mucocutaneous disease.

Based on her clinical history and presentation, in addition to her histological skin biopsy findings and degree of epithelial detachment, a diagnosis of SJS/TEN overlap syndrome was made. AMOX and antiepileptics were stopped. LEV was identified as a safer alternate AED, and was commenced. In addition to supportive care, IVIG in a dose of 2 g/kg in total and methyl prednisolone 2 mg/kg/day combined treatment were commenced. After the sixth day of treatment her clinical state began to improve. The corticosteroid was tapered and re-epithelization was almost complete in 3 weeks with slight sequelae in the left eye. Six weeks after full recovery, PTs were performed with AMOX, VPA, LTG and LEV.Initial 1% concentration in petrolatum was negative for all; however, after increasing the concentration to 20%, LTG resulted in a 3 (+) reaction and other drugs tested remained negative after increasing the concentration to 30%. She has since remained tolerant of LEV but has a residual corneal abrasion.

Recommended diagnostic approach to HRs to AEDs in children

The main differential diagnosis of HRs to AEDs in children is a viral infection. The diagnosis of AED HRs is made on the basis of detailed history, clinical findings, skin tests (PTs, delayed-reading IDTs), LTT and/or a DPT. These investigations are ideally performed 6 to 8 weeks after complete recovery of the initial reactions. An algorithm for diagnosis and management of AEDs induced HRs in children is proposed(Figure 5).

Conclusion

AEDs are commonly required in the management of epilepsy in children and are usually taken on a daily basis over many months to years, depending on the underlying seizure disorder and if there is a treatable cause. The vast majority of AED treatment regimens are well tolerated, but *de-novo* HRs are increasingly reported. The diagnostic work up of HRs where an AED is suspected as the trigger can be challenging as there is often an ongoing clinical need for an AED medication, reactions can be severe and life-threatening, and current tests have not been rigorously validated.The primary goal in the diagnosis and management of HRs to AEDs should be trying to accurately identify the causal trigger and simultaneously identify a safe and effective alternate AED. There is therefore an

ongoing need to improve our knowledge of HRs due to AED medications and in particular to improve and develop our diagnostic capabilities.

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