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Cross-reactivity of skin rashes with current antiepileptic drugs in Chinese population

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ABSTRACT

Objective: Due to less experience with the cross-reactivity of antiepileptic drugs (AEDs) in Chinese population, we surveyed the rates of cross- reactivity of rash among commonly used AEDs in Chinese patients with epilepsy, particularly between the traditional and the new compounds.

Methods: We have retrospectively reviewed the medical records concerning all antiepileptic drug treatment in consecutive Chinese patients with epilepsy in our center. The incidence of AED-related rash was determined in 3793 outpatients, taking at least one of the AEDs-carbamazepine (CBZ), valproic acid (VPA), phenytoin (PHT), phenobarbital (PB), clonazepam (CZP), oxcarbazepine (OXC), lamotrigine (LTG), gabapentin (GBP), topiramate (TPM), levetiracetam (LEV) and traditional Chinese medicine (TCM). We have performed telephone interviews among all patients with AEDs-related rash. We described the clinical characteristics of the 18 patients with cross-reactivity involving the AEDs, and the cross-reactivity pattern for CBZ, PHT, OXC, and LTG.

Results: A total of 3.61% (137/3793) of patients experienced a skin rash to at least one AEDs, of these patients, 73 (53.28%) were female and 64 were males (46.72%). While 18 patients had a rash to two or more AEDs. Of patients who had a rash to CBZ and were also prescribed PHT ($n = 17$), 52.9% had a rash to PHT (abbreviated as CBZ → PHT: 52.9%); of patients who had a rash to PHT and were also prescribed CBZ ($n = 13$), rate of rash was 69.2% (i.e., PHT → CBZ: 69.2%). Other results: CBZ → LTG: 25% ($n = 16$); LTG → CBZ: 44.4% ($n = 9$); CBZ → OXC: 40% ($n = 10$); OXC → CBZ: 66.7% ($n = 6$); LTG → PHT: 20% ($n = 5$); PHT → LTG: 16.7% ($n = 6$); OXC → LTG: 25% ($n = 4$); LTG → OXC: 33.3% ($n = 3$); OXC → PHT: 25% ($n = 4$); PHT → OXC: 16.7% ($n = 6$). There was a highly significant mutual risk for cross- reactivity for CBZ and PHT, and OXC, and LTG ($p < 0.001$), mutual risk reached statistical significance for LTG and CBZ ($p = 0.01$).

Conclusion: Cross-reactivity rates between certain AEDs are high, especially when involving carbamazepine and phenytoin. There were also too few patients with rash to reach definitely conclusions about possible cross-reactivity. Larger numbers of patients would be needed to assess this and the mechanism. Caution should be exercised when prescribing certain AEDs (especially CBZ and PHT, but also OXC, and LTG).

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1. Introduction

Epilepsy is a serious chronic brain disorder that is characterized by recurrent unprovoked seizures, which in most patients can be successfully treated and controlled with mono- or polytherapy. Rash is a common side effect of antiepileptic drugs (AEDs).[1–3] The rash is most commonly a benign exanthematous eruption, which disappeared within a few days after discontinuation of the drug; however, severe life threatening reactions could occur, such as Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN)[4–7] (characterized by focal or extensive detachment of epidermis and erosions of mucous membranes), and hypersensitivity syndrome[8,9] (characterized by fever, skin rash, and systemic manifestations such as hepatitis and eosinophilia). Benign rash are relatively common with aromatic AEDs (such as phenytoin, carbamazepine, and phenobarbital) with a frequency ranging from 5 to 15% of treated individuals.[1] The relatively new antiepileptic drug oxcarbazepine and lamotrigine are also reported to cause skin rash. Although lamotrigine has a different structure, it has also been frequently associated to rash (8–10%).[10] A high starting dose and a rapid dose escalation have been identified as risk factors, especially for LTG, particularly when its metabolism is inhibited by valproate, and can be reduced with low doses and slow titration. Cross sensitivity among aromatic AEDs occurs in 40–58% of patients[11,12] in vivo and has been reported as high as 80% in an in vitro assay.[13] A rechallenge with a possible cross-reactive AED resulted in hypersensitivity reactions in up to 87% of patients.[14]

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Few reports have studied the frequency of cross-reactivity of skin rashes among a large number of patients taking more than one AEDs. There is less experience with the cross-reactivity of AEDs in Chinese population. The aim of this study was to assess cross-reactivity of skin rashes among current AEDs, including new generation of antiepileptic drugs (OXC and LTG) in Chinese population.

2. Methods

We systematically reviewed the medical records of 3793 consecutive outpatients with epilepsy taking at least one antiepileptic drugs, seen by at least two epileptologists at the Epilepsy Center of PLA General Hospital between February 25,1999, and April 9, 2010. A cutaneous side reaction was defined as any types of rash, no other obvious reason than an antiepileptic drug effect, which only has itching feeling without obvious skin change was excluded. We recorded the clinical description of rashes and all drugs using in all patients. We have performed telephone interviews among all patients with AEDs related-rash and some no rash patients who's documentation was considered insufficient. All patients had at least one office visit or telephone interviews after the occurrence of skin reaction.

We compared the rate of rash attributed to the 11 most commonly used AEDs at our center: carbamazepine (CBZ), valproic acid (VPA), phenytoin (PHT), phenobarbital (PB), clonazepam (CZP), oxcarbazepine (OXC), lamotrigine (LTG), gabapentin (GBP), topiramate (TPM), levetiracetam (LEV) and traditional Chinese medicine (TCM). Cross-reaction was defined as sequential rashes from different AEDs in the same individual.

Data were analyzed using SPSS v.13.0. X^2 or Fisher exact tests were used as applicable, to compare the rates of rash to specific AEDs in patients with and without rash to other specific AEDs. Significance was set at $p < 0.001$, and p value between 0.001 and 0.05 was considered a trend.

3. Results

Overall, 3.61% (137/3793) of patients experienced a skin rash to at least one AEDs, while 13.14% (18/137) patients had a rash to two or more AEDs. As much as 75% of the reactions occurred either to CBZ (42.34%, 58 of 137), LTG (16.79%, 23 of 137), OXC (10.95%, 15 of 137), or PHT (5.11%, 7 of 137) (Fig. 1). Of these patients, 64 were males (46.72%) and 73 (53.28%) were female. Females (4.97%, 73/1470) were nearly twice as likely to develop a rash as were males (2.76%, 64/2323) (OR = 1.84, CI 1.31–2.60, $p < 0.001$). Most patients (83.94%, 115/137) had common maculopapular eruption. 92.70% (127/137) rashes occurred less than three mouths after beginning medication.

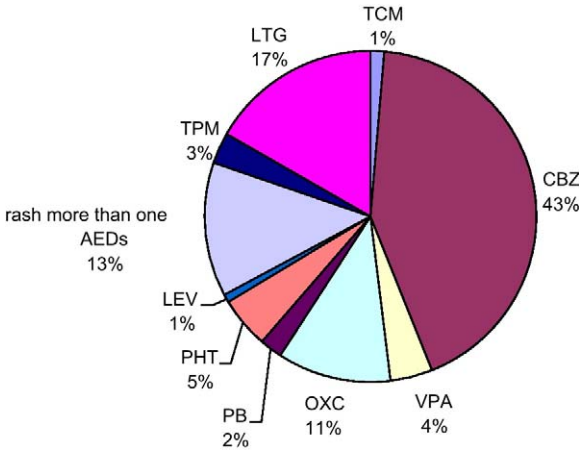

Fig. 1. Diagram of drugs causing skin rash. CBZ: carbamazepine, VPA: valproic acid, PHT: phenytoin, PB: Phenobarbital, CZP: clonazepam, OXC: oxcarbazepine, LTG: lamotrigine, TPM: topiramate, LEV: levetiracetam, and TCM: traditional Chinese medicine.

18 patients experienced more than one AEDs, of whom 11 (61.11%) were females. Clinical characteristics of the 18 patients with cross-reactivity involving the AEDs were showed in Table 1. Five patients experienced skin reactions from more than two drugs. Three subjects reported Stevens–Johnson syndrome, all of them were related to CBZ-SJS. A 41-year-old man had been on medication of CBZ (400 mg daily) for 1 year without rash, however, dyspnea and palpitation occurred after he received antibiotics for influenza. Two months later, the dose of CBZ was increased to 600 mg daily for poor control of epilepsy and skin rash with focal detachment of epidermis (SJS) occurred seven days later. Another 70-year-old man suffered with maculopapular rash and focal detachment of epidermis (SJS) after he had taken CBZ (400 mg daily) for one month. CBZ was then discontinued. Six months later, PHT (300 mg daily) was administered and rash occurred again. Now he is on medication of TPM without any adverse effects. In a 41-year-old woman, rash occurred after she had taken CBZ

Table 1
Clinical characteristic of patients with rash from more than one antiepileptic drugs.

Patient	Sex	Age	First rash	Second rash	Third rash	Fourth rash	Other drugs without rash
1	M	18	CBZ	PHT			LTG TPM
2	M	50	CBZ	PHT	PB	OXC	TPM
3	F	6	CBZ	LTG			PHT, PB
4	F	8	OXC	LTG			TPM
5	F	28	CBZ	PHT			TPM
6	F	30	CBZ	PHT			
7	F	58	CBZ	PHT	TCM		VPA
8	M	15	CBZ	TPM			VPA
9	F	16	CBZ	LTG			TPM
10	F	27	CBZ	OXC			VPA
11	F	18	LTG	VPA			TPM
12	F	40	CBZ	LTG	PHT		TPM
13	M	21	CBZ	PHT			PB, TPM, TCM
14	M	35	CBZ	OXC	TPM		LEV
15	M[a]	41	CBZ	PHT	LEV	GBP	TPM
16	M[a]	70	CBZ	PHT			TPM
17	F	39	CBZ	LTG			TPM
18	F[a]	41	CBZ	OXC			VPA, LEV, TPM

The column to the right shows other drugs used for more than 3 months without causing rash. CBZ: carbamazepine, VPA: valproic acid, PHT: phenytoin, PB: phenobarbital, OXC: oxcarbazepine, LTG: lamotrigine, GBP: gabapentin, TPM: topiramate, LEV: levetiracetam, and TCM: traditional Chinese medicine.
[a] Stevens–Johnson syndrome.

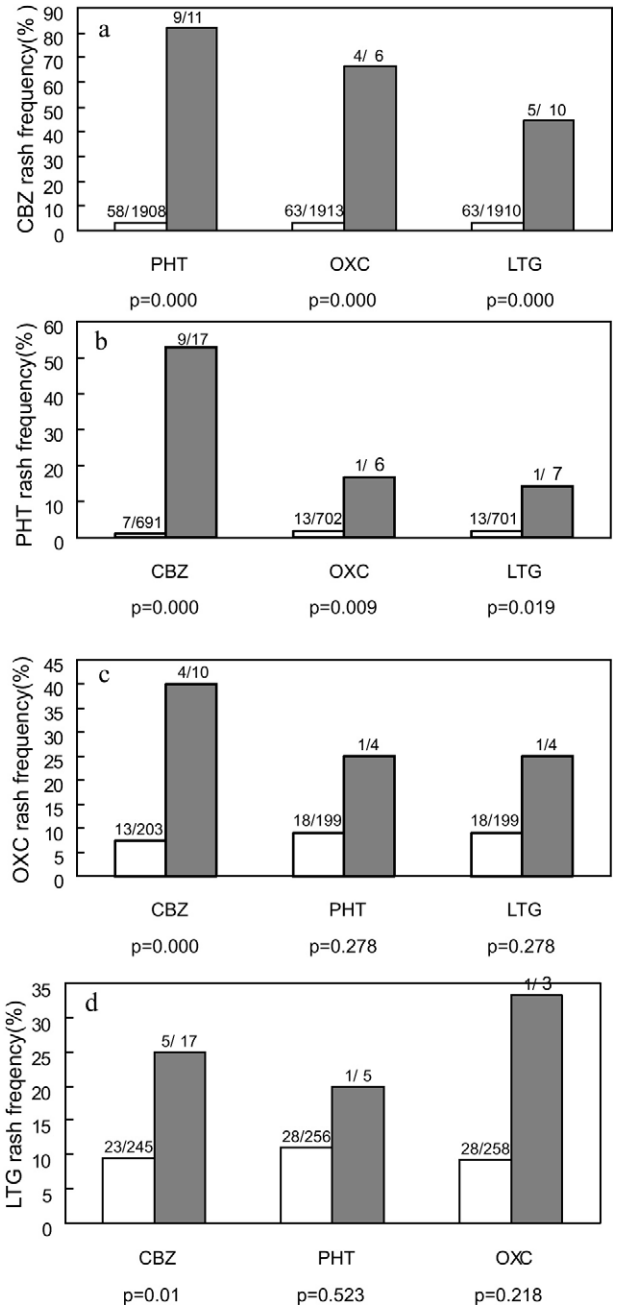

Fig. 2. Cross- reactivity pattern for CBZ (a), PHT (b), OXC (c), and LTG (d). The white columns represent the rash frequency in patients without reactions to the indicated drug, whereas the black columns represent the cross-reactivity rate [e.g. the first bar set represents the following: 58/1908 without rash from PHT (unexposed or exposed) experienced a rash from CBZ, and 9/11 patients with rash from PHT also experienced a rash from CBZ].

(300 mg daily) for one month. However, CBZ was not stoped, the rash aggravated, SJS developed and oral mucosa was afflicted seven days later. The rash resolved after CBZ was discontinued. Three months later, OXC (150 mg daily) was administered and sporadic maculopaular rash reoccurred in face the second day after the medication. OXC was discontinued and the rash resolved, SJS did not occur.

4. Rash cross-reactions rates

The pattern of cross-reactivity is illustrated by bar charts in Fig. 2. Cross-reactions results are studied and abbreviated by the following nomenclature (as an example, to report the rates of cross-reactions between CBZ and PHT): Of patients who had a rash to CBZ and were also prescribed PHT ($n = 17$), 52.94% (9/17) had a rash to PHT (abbreviated CBZ → PHT: 52.94%); of patients who had a rash to PHT and were also prescribed CBZ ($n = 13$), rate of rash was 69.2% (i.e., PHT → CBZ: 69.2%). Other results: CBZ → LTG: 25% ($n = 16$); LTG → CBZ: 44.4% ($n = 9$); CBZ → OXC: 40% ($n = 10$); OXC → CBZ: 66.7% ($n = 6$); LTG → PHT: 20% ($n = 5$); PHT → LTG: 16.7% ($n = 6$); OXC → LTG: 25% ($n = 4$); LTG → OXC: 33.3% ($n = 3$); OXC → PHT: 25% ($n = 4$); PHT → OXC: 16.7% ($n = 6$). It should be pay attention to that the two cross-reactivity rates for each AED pair (CBZ → PHT and PHT → CBZ, for example), does not imply that one drug was prescribed before another, but simply that there was a rash to the first drug, and the second drug was also prescribed (either before of after). There was evidence of specific cross-reaction between CBZ and PHT, and between PHT and CBZ, and between CBZ and OXC, and between CBZ and LTG ($p < 0.001$), with a trend between LTG and CBZ ($p = 0.01$). For example, the CBZ rash rate in patients who also had a rash to PHT (81.81%) was significantly higher compared to without rash from PHT (unexposed or exposed) experienced a rash from CBZ (3.04%). Numbers with PHT, OXC and LTG were too small to reach any meaningful conclusions. Fig. 3 shows detailed data of skin reactions and drug exposures.

5. Discussion

Our result showed 3.61% of patients experienced a skin rash to at least one AEDs, while 18 (13.14%) patients had a rash to two or more AEDs. Carbamazepine (42.34%) was the leading cause of AEDs-rash in our study, followed by lamotrigine, oxcarbazepine, and phenytoin. They usually occur as mild and monosymptomatic maculopapulous exanthemas and only require withdrawal of the offending drugs for resolution. Three subjects reported Stevens–Johnson syndrome, all of them were related to CBZ-SJS, no fatal cutaneous adverse reactions occurred.

Cross-reaction among aromatic AEDs (CBZ, LTG, OXC, PHT, PB) is said to occur in 40–58% of patients. Handoko et al.[15] found that symptoms of hypersensitivity were reported twice as frequently with aromatic AEDs than with non-aromatic AEDs. Our results are generally consistent with these findings, but expand upon them in a larger population ($n = 3793$, but only 18 patients having rash to more than one AED) and involving more AEDs, including the newer ones. On average one in six of our patients who presented with a rash from one of the high risk drugs (CBZ, PHT, OXC and LTG) also developed a rash when exposed to another. Alvestad et al.[16] have retrospective reviewed of 663 patients with epilepsy, skin reactions occurred in 93 patients and sequential rashes related to aromatic drugs in 17 patients. A history of an AED-related rash was significantly associated with reactions to PHT, CBZ, and OXC ($p < 0.001$). The association was only borderline significant for LTG ($p = 0.05$). The largest previously publisher report[17] on cross-reactivity between several AEDs was a retrospective review of 1875 outpatients (≥2 years) exposures to 15 AEDs, 72 of the 1875 (2.8%) patients had a rash to two or more AEDs. Of patients who had a rash to CBZ and were also prescribed PHT ($n = 59$), 57.6% had a rash to PHT; of patients who had a rash to PHT and were also prescribed CBZ ($n = 81$), rate of rash was 42.0%. These results are comparable to ours (CBZ → PHT: 52.94%, PHT → CBZ: 69.2%, respectively).

PHT and CBZ are the two drugs which most frequently cause mutual sensitivity. In this study it occurred with similar rates (50–69%) as in the previous study by Hyson and Sadler[12] (40–58%). We also found a highly significant mutual risk for cross-reaction for CBZ, PHT, OXC, and LTG ($p < 0.001$), mutual risk reached statistical significance for LTG and CBZ ($p = 0.01$). OXC has less potential to

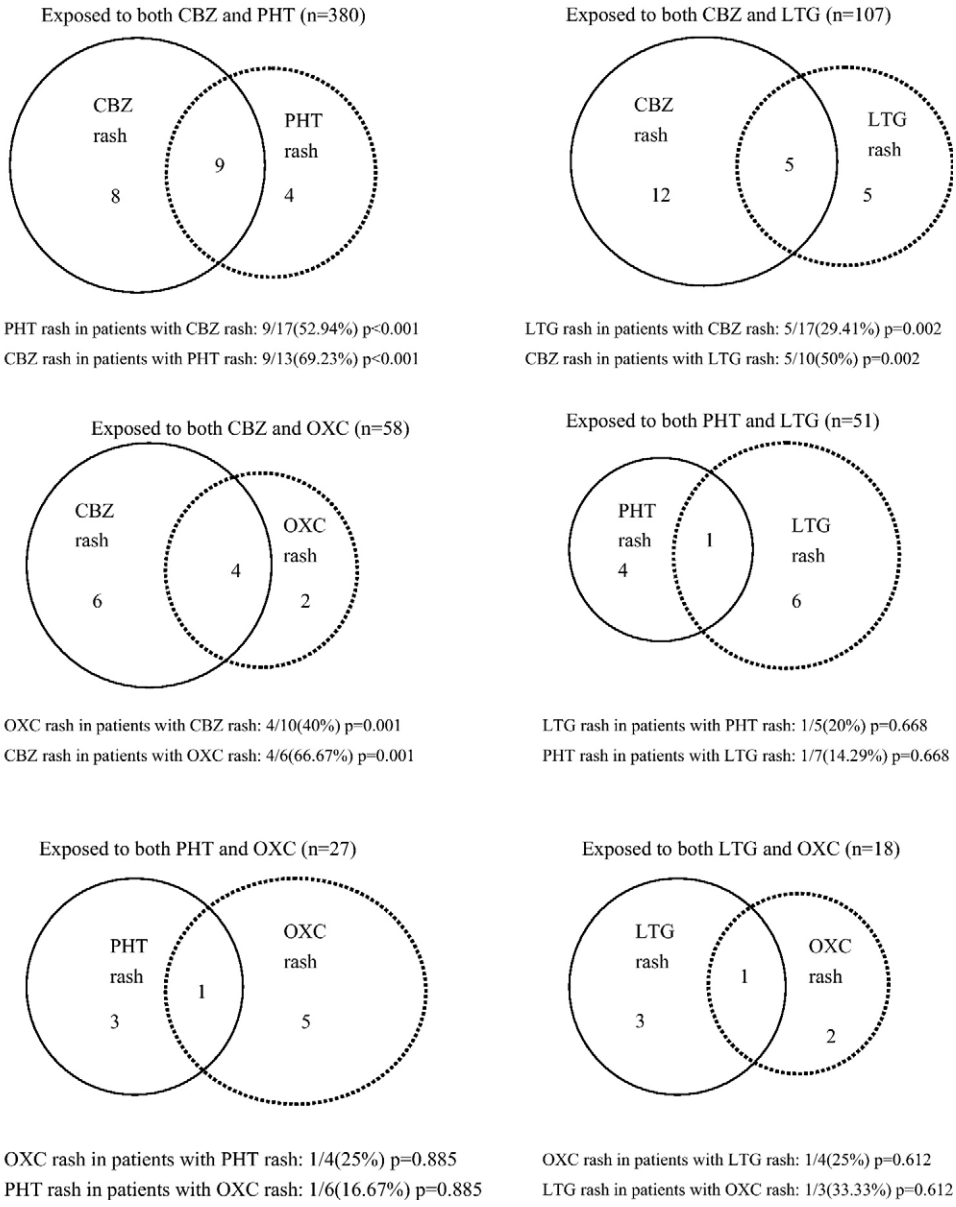

Fig. 3. Venn diagram showing numerical data of cross-reactivity among antiepileptic drugs. The *p* values compare rash rates for each drug in patients exposed to two drugs with and without rash from the other.

cause skin reactions than CBZ,[18] which has been explained by a different metabolic pathway. But the somewhat higher frequency of OXC-related rash in our patients, 8.92%, compared to findings derived from controlled clinical studies (3%).[19] Cross-sensitivities in patients with known rashes from CBZ have been found in the range of 25–31%,[16] our result (40–67%) higher than that (Fig. 3), but there were also too few patients to reach definitely conclusions.

Specific cross- reactivity among CBZ, PHT, and OXC may be at least partially explained by the "hapten hypothesis"[20] that suggests common metabolic and immunologic pathway responsible for rash to there AEDs. CBZ, PHT, and PB are metabolized to arene oxide metabolites by hepatic cytochrome P450 enzymes. There is evidence the CBZ-specific T-cells may exist in peripheral blood of hypersensitive patients many years after resolution of clinical symptoms.[21] Nevertheless, in the last decade, findings from in vitro studies have challenged the classic "hapten hypothesis" by demonstrating that the parent drugs CBZ, PHT, and PB may stimulate T-cell clones even in the absence of any apparent reactive metabolite formation.[22,23] Recently, a strong association was found between Stevens–Johnson syndrome and the HLA B*1502 gene in Han Chinese treated with CBZ.[24] Therefore, to identify genetic polymorphisms predisposing may offer the possibility of avoiding the development of AED-induced severe cutaneous reaction in Chinese patients with epilepsy in the further study.

Our data also show highly significant mutual risk for cross-reactivity rates between CBZ and LTG, these findings are different with other studies which showed lower rash cross- reactivity rates with other AEDs for LTG than for the other aromatic AEDs.[16] Chemically, LTG is also an aromatic compound with two ring structures. LTG can be bioactivated to an arene oxide. It has been hypothesized that this may represent a minor metabolic pathway in humans, which may cause rash. There is evidence that LTG may directly stimulate T-cells in the absence of any apparent hapten formation or antigen processing.[25] Few studies have assessed immunologic cross-reactivity and their results are contradictory.[26]

The mechanisms behind skin reactions and cross-reactivity indeed appear to be complex and diverse. In our study, there were also too few patients with rash to reach definitely conclusions about possible cross-reactivity. Larger numbers of patients would be needed to assess this and the mechanism.

6. Reliability of the study

This study is based on a retrospective analysis, which is the major limitation of it, including a remote history of only vaguely described rashes. Our retrospective approach and the small number of patients in some of the subgroups are apparent weaknesses in this study. Not every rash was examined by a physician. There may have physician bias in making the determination of whether a certain rash was related to a given medication. Recall bias about AED treatment initiated prior to treatment at our center may have resulted in underreporting of prior AED-related rashes in some patients, particularly the old medications (phenobarbital) used decades ago. Some individuals medical records may have been incomplete, but the study was carried out at specialist outpatient clinics served by the same specialists. In our hospital, epilepsy is traditionally treated and followed up by hospital specialists and detailed medical records were available for most patients back to our outpatient department or by telephone interviews. Treatment selection bias may have served to equalize individual AED-rash rates patients with a documented history of AED-rash may preferentially be prescribed AEDs less often associated with rash (e.g., LEV, GBP, TPM, or VPA).

7. Conclusion

To the best of our knowledge, our study is the first one that demonstrated the rates of cross- reactivity of rash among commonly used AEDs in Chinese patients with epilepsy. Cross- reactivity rates between certain AEDs are high, especially when involving carbamazepine and phenytoin. In this study, the cross-reactivity between LTG and the other aromatic AEDs (PHT, and CBZ) was not lower than other aromatic drugs. But there were also too few patients with rash to reach definitely conclusions about possible cross-reactivity. Larger numbers of patients would be needed to assess this and the mechanism. Caution should be exercised when prescribing certain AEDs (especially CBZ and PHT, but also OXC, and LTG).

Conflict of interest statement

The authors have no conflicts of interest that are relevant to the content of this study.

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