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GENETIC FEATURES OF THE DEVELOPMENT OF STEVENS — JOHNSON SYNDROME, INDUCED BY CARBAMAZEPINE

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Introduction

Carbamazepine is the generic name of a widely used type of seizure medicine. An anticonvulsant used to control grand mal and psychomotor or focal seizures. Indicated for pain associated with trigeminal neuralgia; beneficial results have also been reported in glossopharyngeal neuralgia. Carbamazepine is not a simple analgesic and should not be used for the relief of trivial aches or pains.

One rare side effect of Carbamazepine is a serious and potentially fatal skin reaction called Stevens — Johnson syndrome and/or toxic epidermal necrolysis. Stevens — Johnson syndrome is a type IV (subtype C) hypersensitivity reaction that typically involves the skin and the mucous membranes. This serious skin rash usually occurs within the first few months of taking Carbamazepine. People of Asian ancestry who carry a certain gene called the HLA-

B*1502 allele may be at an increased risk for developing this skin rash. This is why before taking Carbamazepine, certain patients (those with ancestry in populations where the gene may be present) will need to undergo a screening genetic blood test. That being said, an absence of the gene doesn't mean a person cannot develop the serious rash. Likewise, having the gene doesn't mean a person will absolutely develop a severe rash.

CBZ-induced hypersensitivity reactions of varying clinical presentation and severity are common and occur in approximately 3–10 % of patients with similar frequencies reported for adults and children. The majority of hypersensitivity reactions are relatively mild skin rashes that often require the discontinuation of CBZ for symptoms to resolve. However, CBZ also causes severe and life-threatening hypersensitivity reactions, which include the Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) spectrum, and drug-induced hypersensitivity syndrome (HSS). SJS/TEN is characterized by a blistering rash and hemorrhagic erosions of mucous membranes, with TEN being the more severe form with more extensive skin detachment. HSS is characterized by a skin eruption, fever, and involvement of at least one internal organ, most frequently the liver. Even though rare, the morbidity and mortality associated with these dramatic hypersensitivity reactions is substantial (long term complications in 45 % and mortality of 2 % in children with SJS/TEN; mortality of up to 10 % for SJS and HSS, and up to 50 % for TEN in adults).

A genetic basis of CBZ-induced hypersensitivity reactions has previously been investigated in primarily adult patients. In these studies, strong associations of two genetic variants in the human leukocyte antigen (HLA) region, HLA-B*15:02 and HLA-A*31:01, with CBZ hypersensitivity were identified. Patients carrying HLA-B*15:02 were shown to be at strongly increased risk of CBZ-induced SJS/TEN. Recent prospective study demonstrated the clinical potential of this pharmacogenetic marker to reduce the occurrence of CBZ-induced SJS/TEN. However, HLA-B*15:02 is observed primarily in certain Asian populations and only very rarely in patients outside of Asia. Correspondingly, a higher incidence of CBZ-induced SJS/TEN in countries where HLA-B*15:02 is common has been suggested. More recently, HLA-A*31:01 was reported to be associated with various CBZ-induced hypersensitivity reactions, including HSS, SJS/TEN and skin-specific maculopapular exanthems (MPE) in European and Asian patients.

Aim

To study the genetic predisposition to the development of Stephen-Johnson syndrome induced by taking Carbamazepine.

Material and research methods

Analysis of foreign sources articles has indicated that, use of a new gene variant test can greatly reduce the incidence of cutaneous adverse reactions to carbamazepine. The study was conducted in Japanese patients, but the test should also be effective in US and European populations and may be warranted in routine clinical practice, the sources say. The research Taisei Mushiroda, PhD, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan, explains that cutaneous adverse drug reactions with carbamazepine are common and problematic, and the most severe — Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) — can be fatal.

A gene variant, HLA-B*15:02, found in the Han Chinese in China, Taiwan, and Hong Kong, and the Thai, Indian, and Malay populations and linked to these adverse reactions, has previously been identified, and genetic testing in these populations is now recommended before carbamazepine is prescribed. Screening for HLA-B*15:02 is mandated in patients from South East Asia because of a strong association with Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

HLA-A*31:01 predisposes to multiple phenotypes of CBZ hypersensitivity including maculopapular exanthema, hypersensitivity syndrome, and SJS/TEN in a range of populations

including Europeans, Japanese, South Koreans and Han Chinese, although the effect size varies between the different phenotypes and populations.

One of the editorialists, Howard L. McLeod, PharmD, Moffitt Cancer Center, Tampa, Florida, told Medscape Medical News, notes that more recently, a second variant — HLA-A*31:01 — linked to cutaneous adverse drug reactions with carbamazepine has been identified in these populations. The current study is the first to proactively test for this gene variant and use it to guide treatment decisions. For the study, neuropsychiatrists were asked to prescribe carbamazepine for patients who tested negative for the HLA-A*31:01 gene variant and alternative drugs for those who tested positive for the variant. Of the 1130 included patients tested, 198 (17.5 %) were positive for HLA-A*31:01and were given alternative medication. Cutaneous adverse drug reactions occurred in 23 of the carbamazepine patients (2.0 %), 4 of whom required hospitalization. No cases of SJS or TEN were seen. The authors say the 2 % figure for carbamazepine cutaneous reactions in this study compares favorably with that in historical controls, which ranges from 3.4% to 5.1%, thus representing a reduction of at least 40 %. They note that the frequency of the HLA-A*31:01 allele is 7 % to 9 % in Japanese, 5 % in Korean, 2 % in Chinese, 2 % to 3 % in European, and 1 % in African populations.

Moreover, the variant has been associated with a full spectrum of carbamazepine-induced cutaneous reactions, and therefore HLA-A*31:01 screening prior to prescribing carbamazepine would be useful for preventing many types of carbamazepine-induced cutaneous adverse drug reactions in a range of patient populations. In Ursula Amstutz research HLA-A*31:01 of European patients given the differences in origin between CBZ cases and controls, we performed a subgroup analysis for HLA-A*31:01 in patients with three or more grandparents of European origin. Twenty CBZ cases and 65 controls were included in this analysis. The frequency of HLA-A*31:01 in European CBZ-tolerant children was similar to the frequency reported previously in a European study. Similar results were observed for the association of HLA-A*31:01 with CBZ hypersensitivity as for the full cohort, with 20 % of CBZ cases carrying HLA-A*31:01. As in the full cohort, a stronger association was observed when only considering patients with CBZ-HSS or MPE.

Conclusion

For patients who test positive for HLA-A*31:01, alternative treatments are available. When alternatives have failed or are unavailable, HLA-A*31:01 testing can alert clinicians to 1) patients who are at increased risk of CBZ hypersensitivity who can then be targeted for more intensive monitoring and 2) increase diagnostic certainty in cases where hypersensitivity has already occurred, so patients can be advised to avoid structurally related drugs in the future. On the basis of the current evidence, we would favor screening all patients for HLA-A*31:01 and HLA-B*15:02 prior to starting CBZ therapy.

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ЭТИОЛОГИЧЕСКИЕ ОСОБЕННОСТИ НОЗОКОМИАЛЬНОЙ ПНЕВМОНИИ В МНОГОПРОФИЛЬНОМ СТАЦИОНАРЕ

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Введение

Нозокомиальная пневмония (НП) является одной из наиболее тяжелых и часто встречающихся госпитальных инфекций. Ее доля в общей структуре нозокомиальных патологий составляет 13–18 %, а уровень летальности остается стабильно высоким [1]. В ряде случаев, терапия НП по-прежнему сопровождается неудачами. Этому способствует широкое распространение антибиотикорезистентных штаммов микроорганизмов, а также ограниченный спектр эффективных антибактериальных препаратов [2]. В связи с этим, на сегодняшний день одной из наиболее актуальных задач при терапии пациентов с НП является своевременное назначение адекватного режима антибактериальной терапии (АБТ), что существенно влияет на исход заболевания [2, 3]. Назначение рациональной АБТ немыслимо без знания этиологической структуры заболевания. Все вышеперечисленное обуславливает необходимость проведения в стационаре регулярного микробиологического мониторинга с целью наиболее раннего выявления возбудителя НП и последующего определения уровня его антибиотикорезистентности.

Цель

Изучить структуру и проанализировать частоту выделения возбудителей НП у пациентов УЗ «Гомельская областная клиническая больница» за 2017 г.

Материал и методы исследования

Произведен ретроспективный анализ медицинской документации (медицинская карта стационарного больного) пациентов, которым был выставлен диагноз НП. Всего за 2017 г. в различных отделениях УЗ ГОКБ с диагнозом пневмонии было пролечено 40 пациентов, у 13 из них пневмония была классифицирована как нозокомиальная. В оставшихся случаях пневмония была определена как внебольничная. Возраст пациентов колебался от 22 до 93 лет. Оценивались результаты микробиологических посевов. Микробиологическому исследованию подвергался биологический материал, полученный в результате бронхоальвеолярного лаважа, трахеальный аспират, а также мокрота пациентов. Качественная характеристика и частота выделения возбудителей НП у пациентов УЗ ГОКБ представлены в таблице 1.

Таблица 1 — Этиология НП пациентов УЗ ГОКБ

Возбудитель НП	Частота выделения
Acinetobacter spp.	21,4 %
Klebsiella pneumoniae	21,4 %
Escherichia coli	14,3 %