

Anticonvulsant hypersensitivity syndrome: a rare and serious complication

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Clinical record

A 22-year-old woman of European ancestry who had a 4-year history of treatment-resistant bipolar disorder presented with symptoms of mania. On admission to hospital, a full blood examination and biochemistry results were normal. Her current doses of lithium (1500 mg daily) and risperidone (2 mg daily) were maintained while treatment with carbamazepine was commenced at 100 mg daily and then increased by 100 mg every 3 days. The patient was discharged from hospital on a regimen of 400 mg carbamazepine daily. Her plasma carbamazepine level at this time was 19 µmol/L (reference range [RR], 16–50 µmol/L). She was in good physical health, and a full blood examination and biochemistry results were normal.

Three weeks after starting to take carbamazepine, the patient developed a mild, barely visible, erythematous maculopapular rash on her arms and chest that disappeared after a few days. She had no other symptoms, and full blood examination and biochemistry results remained normal. After a further 3 weeks, the patient developed marked lethargy, exercise intolerance, muscle aches, night sweats, rigors and a rash. There had been no changes to her medication and she had been complying with her treatment regimen. She lived with her family, and her parents contacted her family general practitioner as well as me (her psychiatrist). She was advised to stop taking carbamazepine, increase the dose of risperidone and seek urgent medical attention. The carbamazepine was stopped over 2 days — 45 days after it was first administered. The family consulted an emergency service on four occasions over 6

days, and the patient was variously diagnosed with contact dermatitis, non-specific allergic reaction, cytomegalovirus and rubella. She was finally admitted to hospital and was found to be febrile (temperature, 38–40°C) and tachycardic (heart rate, 108 beats per minute), with an intensely pruritic maculopapular rash that had spread over most of her body. Her face was swollen, showing periorbital oedema. There was no mucosal involvement or epidermolysis. She had occipital, supraclavicular and inguinal lymphadenopathy, and hepatosplenomegaly. Liver function test results were markedly abnormal (alanine aminotransferase [ALT], 1203 IU/L [RR, < 41 IU/L]; alkaline phosphatase, 156 IU/L [RR, 30–120 IU/L]) and her serum albumin level was low (29 g/L [RR, 35–50 g/L]). She had lymphocytosis (lymphocyte count, $5.9 \times 10^9/L$ [RR, $1.0\text{--}4.0 \times 10^9/L$]), but her C-reactive protein level was not raised. A diagnosis of anticonvulsant hypersensitivity syndrome was made. The patient was transferred to the intensive care unit, where she remained for 48 hours, and treatment with prednisolone 40 mg daily was commenced. Her physical state improved rapidly. After 7 days her ALT level had dropped to < 500 IU/L and she was deemed well enough to be discharged. The prednisolone was gradually tapered by 5 mg per week. Topical betamethasone helped to soothe her pruritus and inflammation, and some mild exfoliation occurred. The patient continued to improve over the next 6 weeks. Her rash disappeared, as did her hepatosplenomegaly, and liver function test results normalised. She recovered fully and has remained on lithium and risperidone. ♦

Anticonvulsants are being used increasingly for mood disorders and chronic pain. Anticonvulsant hypersensitivity syndrome (ACHS) has been reported to occur with use of phenytoin, carbamazepine, phenobarbitone and lamotrigine, but not valproate. It is a rare and potentially fatal complication. ACHS is indicated by the presence of a triad of characteristic clinical features — fever, rash and internal organ involvement. It is estimated to occur in about 1 in 1000 to 1 in 10 000 patients who are exposed to these anticonvulsants.¹ A similar reaction has also been described with exposure to sulfonamides, sulfones, allopurinol and non-steroidal anti-inflammatory drugs (piroxicam in particular).² This reaction has also been referred to as drug-related rash with eosinophilia and systemic symptoms (DRESS) syndrome, and drug-induced hypersensitivity syndrome (DIHS).³

This patient showed a pattern of symptoms quite typical of ACHS, which usually appears after a brief delay of 2–4 weeks after anticonvulsant exposure, but may appear up to 12 weeks later.¹ Her symptoms began to emerge about 6 weeks after she commenced taking carbamazepine, although a mild rash appeared after 3 weeks. Transient rashes are quite common following initiation of carbamazepine therapy and are not an indication for stopping the drug.

Clinicians often fail to consider a diagnosis of ACHS.⁴ Although the seriousness of the illness was initially not obvious, it was fortunate that administration of carbamazepine had been stopped

as soon as significant symptoms began to emerge. It is noteworthy that the patient's physical state continued to deteriorate following withdrawal of carbamazepine, and only improved 1 week later, after hospital admission and treatment with prednisolone. Her mental state did not worsen during her acute illness, and she showed great resilience. Prednisolone has potent mood-altering properties and presents a significant risk for inducing either depression or mood elevation. Close monitoring of mental state and psychiatric involvement is recommended.

Carbamazepine has been linked with a variety of hypersensitivity reactions, ranging from mild and benign urticaria and erythematous maculopapular eruptions to Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). ACHS is usually not as serious as SJS or TEN but can be life-threatening, and deaths from it have been reported.⁵ The skin condition can be extensive in ACHS, but is not as severe as the detachment of body surface area seen with SJS or TEN, which often involves gastrointestinal or tracheobronchial epidermal surfaces.

Genetic factors predispose individuals towards the development of these reactions, and recent data have linked human leukocyte antigen allele B*1502 as a marker in Asian populations, except among people of Korean and Japanese ancestry. Genotyping is recommended for at-risk groups,⁶ the prevalence of the allele is negligible in other ethnic groups.⁶ ACHS is associated with complex immunological changes that include chemotoxic and

Lessons from practice

- Anticonvulsant hypersensitivity syndrome (ACHS) is a rare and potentially fatal complication of treatment with the anticonvulsants phenytoin, carbamazepine, phenobarbitone and lamotrigine.
- Diagnosis is clinical and based on a triad of features: fever, rash and internal organ involvement.
- Early suspicion of diagnosis is essential, as the critical component of treatment is cessation of the implicated drug.
- Pharmacogenetic testing for the human leukocyte antigen allele B*1502 should be considered before commencing carbamazepine in patients of Asian ancestry. ◆

T-cell-mediated inflammatory injuries to tissues containing cytochrome oxidases.² Viral infection may increase an individual's vulnerability.⁷

The most critical component of management of ACHS is discontinuation of the implicated drug.¹ All clinicians who prescribe anticonvulsant drugs therefore need to be aware of ACHS and the requirement for early suspicion of the diagnosis. General supportive measures and systemic corticosteroids are usually given, which in most instances results in full recovery. There is cross-sensitivity among aromatic anticonvulsant drugs (phenytoin, carbamazepine, phenobarbitone and lamotrigine), which means that patients who have had ACHS should avoid all of these drugs.⁴ In addition, a familial association with ACHS exists, and family members of these patients need to be informed that they may be at increased risk of developing this syndrome. Anticonvulsant drugs that are generally considered safe are valproate and benzodiazepines.⁴

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Competing interests

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