

LIFE CLAIMING ANAPHYLAXIS TO INTRAVENOUS CEFTRIAZONE AFTER NEGATIVE SKIN TEST

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SUMMARY

Antibiotic prophylaxis before surgical procedures is commonly practiced. Hypersensitivity reactions to antibacterial drugs are most feared complications, which have varying grades of presentation. Skin testing are commonly applied to detect allergy but that can have false negatives. We report a case of severe anaphylaxis leading ultimately to fatal outcome after negative skin testing. Prior history of allergy of any kind and exposure to ceftriazone was excluded. Even the best antishock management could not help. This observation clearly demonstrates the limit of screening tests for the diagnosis of sensitization against drugs.

KEY WORDS

Ceftriazone, Hypersensitivity, Skin test

Appropriate antibiotic prophylaxis for surgery promises better safety to the patients. Such measures claiming the life of the patients well before operation can make physicians and relatives stunned. Intravenous ceftriazone is generally well tolerated. Hypersensitivity reactions are most feared adverse event attributed to penicillin, imipenem, cilastatin and cephalosporins¹. Severe anaphylactic reactions to ceftriazone not responding to best resuscitative measures ultimately claiming the life of the patients have not previously been reported in the medical literature.

CASE REPORT

52 years old male, weighing 91 kg, police officer by profession, known controlled hypertensive presented to the department of surgery with bilateral varicose veins in the lower limbs. Preanaesthetic evaluation did not reveal any other finding and history of allergy of any kind was denied. Prior exposure to cephalosporins and penicillin were denied. Another cause toxic or infectious could not be ruled out. Patient was planned for stripping of the varicose veins of right leg under spinal anaesthesia. As per the practice at our institute, on the night prior to operation skin testing for ceftriazone was done (with 2mg/ml in normal saline) which yielded negative reaction beyond doubt compared to normal saline negative control. In the operation theatre on the scheduled date all the vegetative parameters were within normal limits. Intravenous access was

secured and preloading was done with 1 L of ringers lactate solution. 1 gm of Ceftriaxone (MONOCEF, Aristo; India) was to be given for antibiotic prophylaxis. Slow I.V. infusion was under progress and about 200 mg of drug had been infused when the patient complained of swelling in throat, pain at the site of injection (suspecting hypersensitivity the infusion was stopped immediately) and restlessness; respiration became laboured and peripheral pulses became feeble. Resuscitative measures were taken with intubation, I.V. adrenaline (0.5 mg diluted to 10 ml and slowly given), volume expansion with normal saline, adrenaline infusion 3µg/min gradually increasing to 5 µg/min till adequate blood pressure was achieved, 100% oxygen, hydrocortisone 200mg, intravenous aminophylline (loading and maintenance) etc. Despite the best efforts highest SPO2 recorded was 10 % (although this value is misleading, since these monitors are not calibrated down to these levels) and blood pressure was normalized within three minutes. ECG never confirmed asystolic cardiac arrest. The patient was shifted to ICU where he was put on elective mechanical ventilation and intensive medical care. After 48 hours he was weaned off the ventilator and extubated. It was found that he had suffered hypoxic encephalopathy. Axial T2 weighted images revealed subtle increased signal involving the thalami, caudate nucleus and lentiform nuclei (Figure1&2). Diffusion weighted scans revealed increasing signal within the thalami on increasing the 'b' gradients with reduction in signal on ADC maps, suggesting cytotoxic oedema. Similar signal changes were also noted involving some of the gyri. MR finding suggested cerebral anoxic damage. Mast cell tryptase was 42.5µg/L on analysis (lab reference 0-14µg/L). Reaction due to any other chemical was not suspected since the vials of injection contain only sodium Ceftriaxone. This along with clinical presentation after injection confirmed anaphylactic reaction. Skin testing was repeated after 2 days of the event, which was again negative. On Glasgow Coma Scale he was M₂V₁E₄. Despite repeated counselling medical team had to suffer wrath of attendants of the patient. Consent for tracheostomy was denied; hence airway was secured by endotracheal intubation. Patient expired on 7th day.

DISCUSSION

For a low molecular weight chemical (as are most antibiotics), to cause an allergic reaction it or its metabolic product usually act as hapten combining with endogenous protein to form an antigenic complex. Such antigens induce the synthesis of antibodies usually after a latent period of at least one or two weeks. Subsequent exposure of the organism to the chemical results in antigen-antibody interaction that provokes the typical manifestation of allergic reaction.² There is no evidence that any single cephalosporin is more or less likely to cause hypersensitivity.¹ Because of similarity in structure of the penicillin and cephalosporins patients who are sensitive to one class of agent may manifest cross reactivity when a member of another class is administered. There is no skin test that can reliably predict whether a patient will manifest an allergic reaction to cephalosporins.³ The correlation between the skin prick test responses and radioallergosorbent test (RAST) for allergen specific serum IgE is

fairly good⁴ but not cent percent. RAST detects the serum level of IgE specific for a given antigen. The allergen is coupled to beads or discs, the patients' serum is added and unbound antibody is washed away. The amount of specific IgE bound to the solid phase allergen is then measured by adding I¹²⁵ labelled rabbit anti-IgE washing the beads and washing the bound radioactivity. The allergen is covalently coupled to immunosorbent, in this case a paper disc, which is then treated with patient's serum. The amount of specific IgE bound to paper can now be estimated by addition of labelled anti-IgE.⁵

Failure of skin test to detect ceftriaxone-specific IgE and consequent untoward reaction has been observed.⁶ The advantage of skin test is that it is relatively inexpensive and allows screening of large number of allergen at one time. The disadvantage is that it sometimes sensitizes the allergic individuals to new allergen and in some rare cases may induce systemic anaphylactic shock. In some instances intranasal challenge with allergen may provoke a response even when both these tests are negative probably due to local synthesis of IgE antibodies. It is impractical to subject every individual to RAST before administration of every drug. Immunodiagnostic tests are at present only readily available for IgE mediated penicillin allergy. Negative skin test indicates that the risk of life threatening reaction is extremely low.⁷ Fatal outcome of this case despite negative skin test indicates that immunological principles have their own limitations.

Another difficulty with predictive tests concerns their predictive value in general. Indeed in this situation the prevalence of the disease in healthy unselected patient is low; as a consequence the predictive value of the test will be minimized, and will lead to an unacceptable rate of false positive and negative results.

Varying grades of anaphylaxis to ceftriaxone in various situations have been reported⁸⁻¹⁶ with evidence of cross reactivity^{8,9,14,15} with other cephalosporins and non-reactivity.^{3,14,16} After penicillins, cephalosporins are most important beta lactams inducing IgE mediated reaction. Responses may be selective or cross reactive with common beta lactam determinants. Unlike determinants derived from benzylpenicillins, cephalosporin allergic determinants have not been properly identified even though these beta lactams is currently used.

Ceftriaxone being commonly used antibacterial drug at our centre, such anaphylaxis of severe grade is rare. Even after recognition the management of the case was in the hands of anaesthesiologists, who are considered most experts to handle such emergencies. We believe that although patients' fatality in our own hands was difficult to explain to the patient's relatives and the hospital administration, it was extremely difficult or nearly impossible with present understanding of immunology, to predict such an accident on the basis of history and possible clinical tests. There was possibility of sensitization due to environmental exposure or to other type of exposure due to ceftriaxone analogues. Dose-response relationship is usually not apparent for the provocation of allergic reactions. Even if some immunological tests eg. RAST are made available, shall the cost and the time consumed justify to detect such

fatality which is extremely rare? Moreover some limitation on the sensitivity of that test would miss some rare case which applies to all diagnostic tests. Further, even if such tests are made available and applied practically, can that make the false negatives to absolutely zero? If not, then we will have to face such rare complications, rarely.

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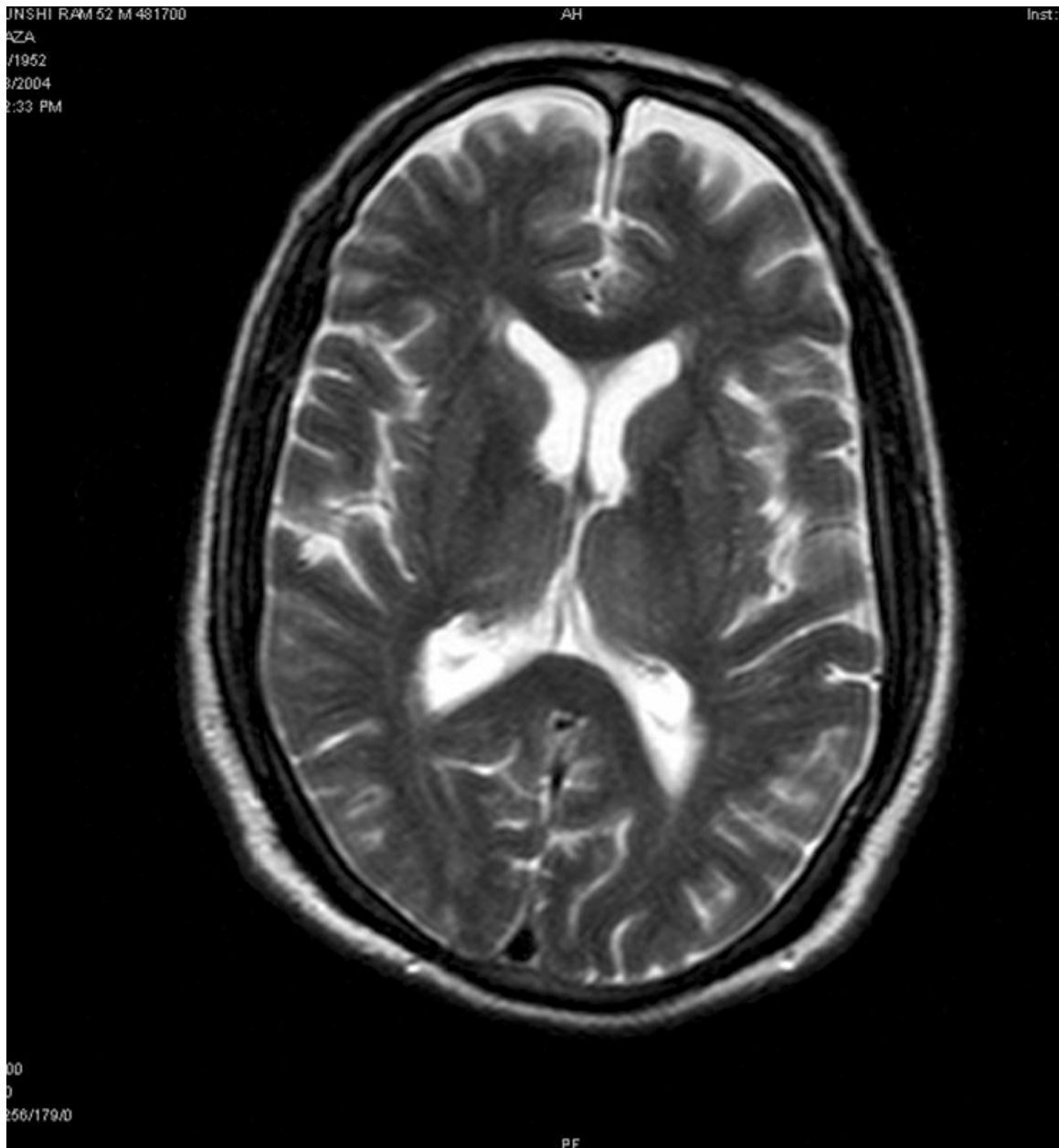


Figure – 1

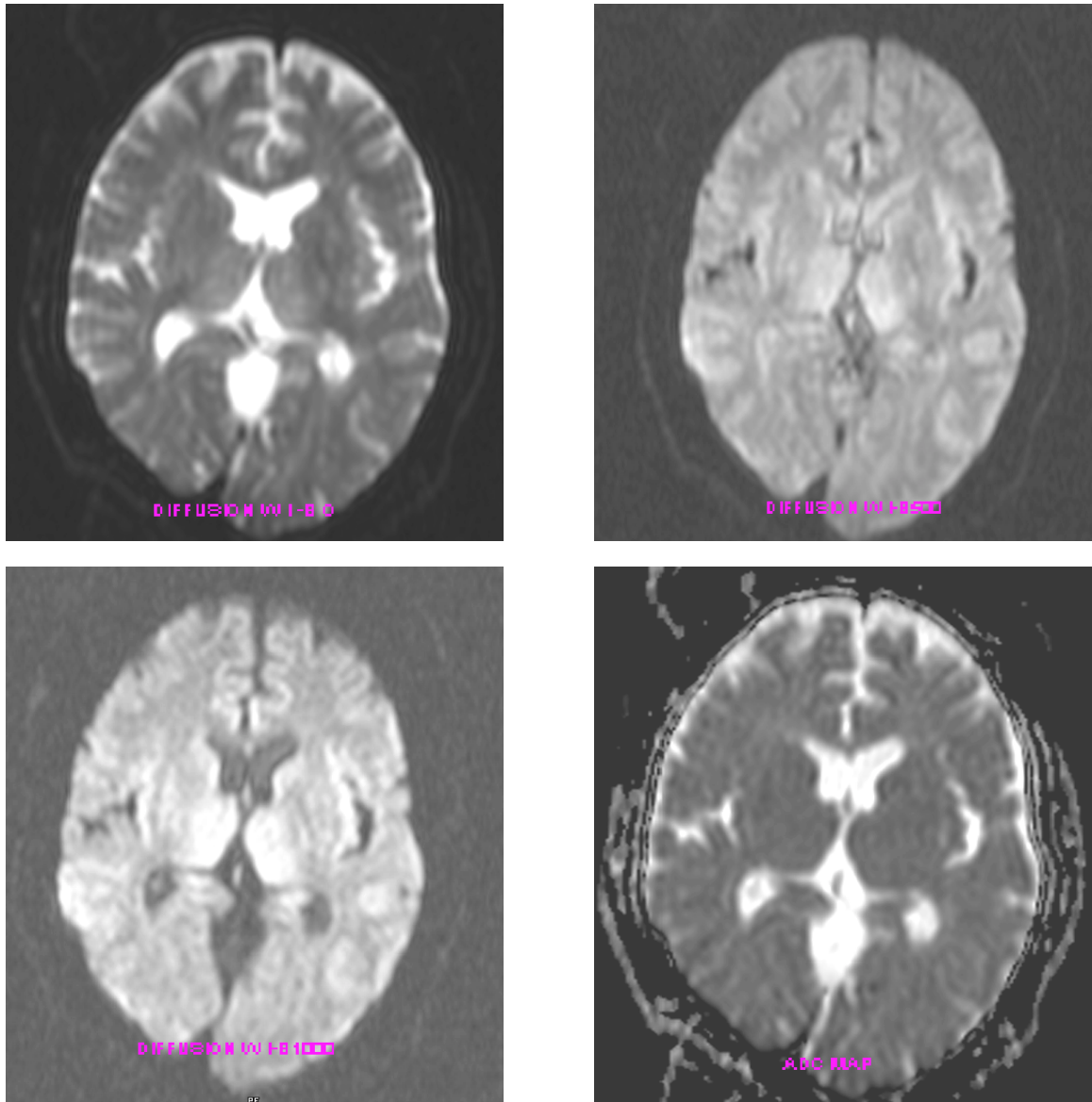


Figure - 2