

Role of Autoerythrocyte Sensitization Test in the Diagnosis of Recurrent Spontaneous Bruising

Abstract

Introduction: Psychogenic purpura, also known as autoerythrocyte sensitization syndrome, is a rare condition which is characterized by spontaneous development of painful purpura, or ecchymoses. Skin lesions are usually preceded by stress and emotional trauma. It is usually a diagnosis of exclusion after ruling out history of trauma, drug intake and other bleeding disorders. Autoerythrocyte sensitization test (AEST) and a psychiatric evaluation helps in the diagnosis and treatment. **Objective:** To demonstrate the importance of AEST in diagnosing the patient of Gardner Diamond syndrome. **Materials and Methods:** Five suspected cases of autoerythrocyte sensitization syndrome underwent AEST after ruling out other causes of bleeding. **Results:** Four out of five patients were positive for AEST while one patient was negative. Psychiatric complaints were present in three patients. One patient was lost to follow up. Rest all patients responded well to vitamin C supplementation. **Conclusion:** Autoerythrocyte sensitization syndrome is a rare disorder and is a diagnosis of exclusion, so a thorough workup of the patient to rule out common causes of bruising is essential. A high index of suspicion on the clinician's part and a simple OPD-based AEST may help in the diagnosis. Psychiatric consultation is important to find out the stress factor and timely management.

Keywords: Autoerythrocyte sensitization test, psychogenic purpura, psychosomatic disorders, spontaneous bruising

Introduction

Autoerythrocyte sensitization syndrome (AES) was described by Gardner and Diamond in four females with recurrent spontaneous bruising in 1955. They suggested that patients get sensitized to extravasated red blood cells (RBCs).^[1] Gardner–Diamond syndrome (GDS) is almost exclusively seen in females; only a few male patients have been reported till now. It is usually associated with psychological stress in the form of hysteria, anxiety, and depression. Still, the exact cause and pathogenesis is an enigma. Over the years, many possible hypotheses have been put forward, but so far, the most accepted theory is its association with psychological stress and autosensitization to RBC membrane antigen phosphatidylserine and soluble hemoglobin.^[2] Here, we are describing a case series of five patients diagnosed with autoerythrocyte sensitization syndrome.

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Report of Cases

Case 1

A 13-year-old female presented with a history of painful, recurrent, spontaneous bruising on bilateral arms, legs, and trunk for the last 2 years. On examination, the patient had no active lesions. Relevant investigations ruled out common causes of ecchymoses. Autoerythrocyte sensitization test (AEST) showed no reaction at 30 min and showed positive results at 4 h. Psychological consultation showed no stress factors, and she was started on vitamin C supplementation. On a 3-month follow-up, the patient showed improvement and no new episode of bruising was noted in the patient.

Case 2

A 32-year-old female presented with recurrent, tender ecchymoses on bilateral arms and legs for the last one year. The patient gave a history of abortion one year back, and attention-seeking behavior was

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noted. On examination, tender ecchymoses were seen over the right shin and left forearm. Laboratory investigations like platelet count, bleeding and clotting time, prothrombin time (PT), partial thromboplastin time (aPTT), International normalized ratio (INR), and antinuclear antibody titer were within normal limits. AEST was positive at 30 minutes, 24 hours, and 48 hours on both whole blood and washed RBC (WRBC) sites, with relatively more tenderness at the WRBC site. She was diagnosed with generalized anxiety disorder and insomnia after a psychiatric evaluation. The patient was advised escitalopram and vitamin C. Monthly follow-up for the next 3 months showed improvement with no new bruising.

Case 3

A 22-year-old female presented with self-resolving episodes of painful bruises for the last 2 years. The patient gave a characteristic history of all the episodes of bruises coinciding with emotional stress due to abortion and lack of support from family after the marriage. The recent episode occurred after the demise of her in-laws. At presentation, she had ill-defined brownish macules on her right leg and bluish-black painless macules on the right arm. After ruling out other causes, AEST was done which was negative at 30 min but showed positive results at 24 hours. Psychological evaluation confirmed generalized anxiety disorder in the form of anger outbursts and free-floating anxiety. The patient was managed on escitalopram, clonazepam, and vitamin C. Monthly follow-up for the next 3 months showed improvement with no new onset bruising.

Case 4

A 23-year-old female presented with a complaint of painful bruises over her thighs and left arm for the last 3 months [Figure 1]. Relevant laboratory investigations were all within normal limits. The patient looked anxious and her attendant gave a history of multiple hospital admissions during the COVID-19 pandemic without any significant symptoms. AEST was positive. Her psychiatric features were suggestive of somatization disorder, and the patient was advised psychiatric consultation. She was started on vitamin C but was lost to follow-up.

Case 5

A 32-year-old female, a known case of acute telogen effluvium, seborrheic capitis, and chronic urticarial complained of spontaneous bruising associated with mild pain over the right thigh for the last 2 years. Each episode lasted for 10 days and recurred after every 3 months. There was no history of psychological stress prior to bruising, but the patient was anxious having various vague complaints. On examination, no active lesions were present. Laboratory investigations were within normal limits. AEST was done and no tenderness or ecchymoses was seen after 24 hours. She denied psychiatric referral and was provisionally



Figure 1: Spontaneous ecchymosis over the right thigh in case 4

diagnosed with GDS and was prescribed vitamin C and was followed up closely for any new lesions. However, no new lesions were seen after 4 months of follow-up.

Discussion

AES, also known as GDS or psychogenic purpura, is a rare autoimmune vasculopathy. The patients usually have normal coagulation parameters, and the skin biopsy findings are nonspecific. The investigations to be performed in AES patients to rule out other disorders are hematocrit, peripheral smear, erythrocyte sedimentation rate, electrolytes, PT, aPTT, bleeding time, and coagulation factors.^[2] The onset may be associated with a prodrome of malaise, fatigue, burning sensation, or pruritus, followed by cutaneous induration. Bruises tend to appear more frequently on the extremities and trunk, although any body part including the face can be involved.^[3]

Its pathogenesis has been proposed as a synergism between the psycho-immunology and mechanical injury of the skin in which preexisting psychosomatic disturbances may affect the skin's immunological function and weaken the dermal capillaries so that even a mild injury to the skin can damage the capillary walls and eventually result in the permeation of RBCs.^[4] It

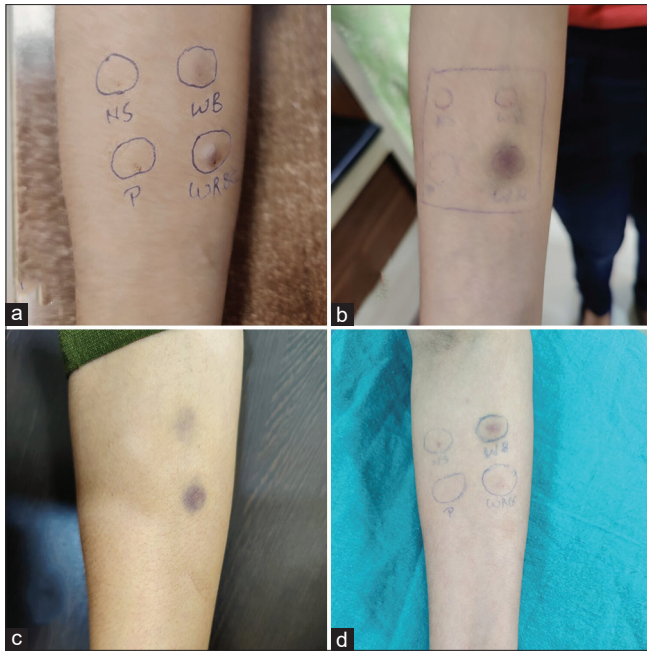


Figure 2: (a) Well-labelled AEST site over the right forearm at the time of injection (b) Ecchymoses and tenderness after 24 hours at washed RBC site indicating positive AEST in case 1 (c) Ecchymoses at both whole blood and washed RBC site after 24 hours indicating positive AEST in case 3 (d) No ecchymoses at washed RBC site denoting negative AEST in case 5

has been observed in association with emotional stress, hysteria, masochism, egoistic characters, emotional liabilities, self-mutilating behavior, aggressive behavior, depression, dissociative disorders, convulsions, hallucinations, and syncope.^[5]

AEST is performed to confirm the RBC antigenicity. The test is performed by intradermal injection of WRBC on the flexural aspect of the forearm [Figure 2]. Steps to prepare WRBCs are depicted in Figure 3.^[6] Conventionally, test readings are taken at 30 min and 24 h. Tenderness or ecchymosis at the injection site is considered positive.^[1] We injected saline as the negative control, whole blood as a positive control, and plasma to rule out the possibility of soluble antigens.

In the present case series, the patients did not have any coagulation or platelet abnormality. Three of them had a definite history of psychological disturbance prior to the episode of spontaneous bruising. The clinical description matches the typical painful bruising on accessible areas, seen in females prone to psychological stress as proposed by Gardner and Diamond.

Various medications like antihistamines, corticosteroids, antidepressants, hormones, and vitamin have been tried for the management of GDS with variable success. Some researchers have explored the role of medications affecting capillary tone or permeability of vessels in the treatment of GDS.^[2,7] As it is a psychological disease, the placebo effect has been used successfully to alter the severity of

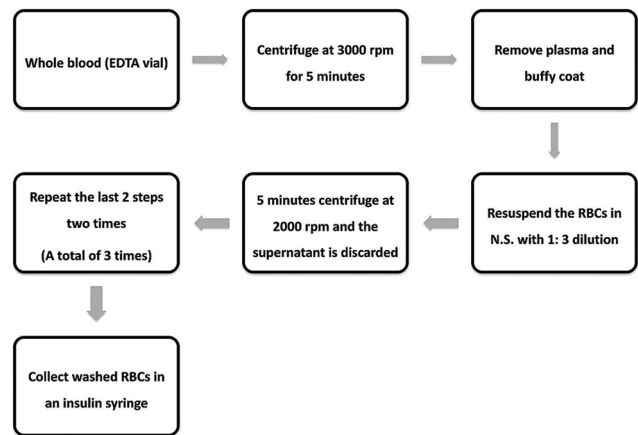


Figure 3: Steps to prepare washed RBC^[6]

symptoms. Psychotherapy and psychiatric treatment are of much help in young age groups such as children and adolescents.^[8] In our case series, four patients responded to oral vitamin C (ascorbic acid 500 mg/day) along with psychiatric treatment whenever warranted. Vitamin C could be helpful in the treatment of AES as it decreases vascular fragility by stimulating collagen synthesis through procollagen hydroxylation, tightens the endothelial cell permeability barrier, and acts as a scavenger of free radicals in endothelial cells.^[9] This further adds to the role of capillary fragility and RBC extravasation in the pathogenesis of AES.

Previously, AES has been described as psychogenic purpura owing to its presence in stress-prone females.^[10] Our findings further reaffirm that psychological stress is an important factor in the pathogenesis of AES. Not all the AEST showed positive results, suggesting that positive ecchymoses are due to RBC antigenicity and not a normal occurrence in response to WRBC injection [Table 1]. AEST also has its limitations as there is no standardization of the test, and it can be negative as has been seen in case 5 in the present study. It is of utmost importance not to label these patients with AES or psychogenic purpura in haste. It is a disorder of exclusion and should be treated like that only. The differential diagnosis includes systemic lupus erythematosus, systemic amyloidosis, dermatitis artefacta, disseminated intravascular coagulation, idiopathic thrombocytopenic purpura, and Henoch–Schoenlein purpura, Ehlers–Danlos syndrome, Munchausen’s syndrome, cellulitis, and compartment syndrome.^[3,11,12] This mandates a thorough workup and further establishing the psychological stress before diagnosing the condition.

Conclusion

AES is a rare disorder and is frequently missed in outpatient evaluation. This often leads to patients undergoing multiple tests to identify the cause of painful bruising which further

Table 1: Clinical profiles of the patients.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age/Sex	13/F	32/F	22/F	23/F	32/F
Duration	2 years	1 year	2 years	3 months	2 years
Distribution	B/L arms, leg, trunk	Right leg, left forearm	Right leg, right arm	B/L thighs and left arm	Right thigh
H/o Trauma	None	None	None	None	None
Lab investigations	Normal	Normal	Normal	Normal	Normal
AEST	Positive	Positive	Positive	Positive	Negative
Psychiatric complaints	Normal	Generalized anxiety disorder	Anger outburst, free floating anxiety	Somatization disorder	Normal
Treatment	Vitamin C supplementation (Ascorbic acid 500 mg OD)	Vitamin C supplementation (Ascorbic acid 500 mg OD)	Vitamin C supplementation (Ascorbic acid 500 mg OD)	Vitamin C supplementation (Ascorbic acid 500 mg OD)	Vitamin C supplementation (Ascorbic acid 500 mg OD)
Follow-up	3 months	3 months	3 months	Lost to follow up	4 months

adds to the psychological distress. As it is a diagnosis of exclusion, a thorough workup of the patient to rule out common causes of bruising is essential. Psychiatric consultation is important to find out the stress factor and for patient management which hinges on psychotherapy and timely initiation of selective serotonin reuptake inhibitors. A high index of suspicion on the clinician's part and a simple OPD-based AEST may help the patient and provide relief.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

None.

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