Improvement of renal function in epidermolysis bullosa patients after gluten free diet: two cases

G. ANNICCHIARICO1, M.G. MORGESE2,3, L. BRUNETTI4, M. TAMPOIA5, L. GAROFALO6, G. ACETO4, T. FIORE7, S. MAURO8, M. MINELLI9

1Regional Coordination for Rare Diseases, Ares Puglia, Bari, Italy
2Specialty School of Hospital Pharmacy, University of Bari A. Moro, Bari, Italy
3Department of Experimental and Clinical Medicine, University of Foggia, Foggia, Italy
4Department of Biomedicine of Developing Age, B. Trambusti, University of Bari A. Moro, Bari, Italy
5Department of Clinical Pathology, City Hospital Policlinico di Bari, Bari, Italy
6Department of Dermatology, University of Bari A. Moro, Bari, Italy
7Department of Anaesthesia and Intensive Care, University of Bari A. Moro, Bari, Italy
8Department of Genetics, Hospital of Lecce Vito Fazzi, Lecce, Italy
9IMID Center, Department of General Medicine, Campi Salentina, Lecce, Italy

Abstract. – Epidermolysis bullosa (EB) is a rare inherited genetic disease characterized by an abnormal response of the skin and mucosa to mechanical trauma. Dystrophic EB (DEB) is very often associated with many extra cutaneous complications. Those complications involve either epithelial associated tissues or other organs. In particular, several renal complications have been described for DEB in the recessive form, such as amyloidosis, post-infection glomerulonephritis, upper and lower urinary tract obstruction and IgA-Nephropathy (IgAN). In the cases reported below we have two patients diagnosed with DEB that showed compromised renal function and proteinuria. The switch of the normal diet toward a gluten free diet resulted beneficial for both patients, since renal function was rescued and proteinuria cured. Moreover, a general health status improvement was recognised, given that nutritional condition was ameliorated and bone growing enhanced. Furthermore, in both patients the presence of autoantibodies anti-COL7 indicating an autoimmune form of the disease. Therefore, patients received low doses of betametasone useful to reduce inflammatory state and to control immune system function. In conclusion, our results prompt us to hypothesized that in these patients, due to the fragility of the intestinal mucosa, the absence in the diet of gluten may be beneficial.

Key Words: Epidermolysis bullosa, Gluten free diet, Inflammation, Renal complication.

Introduction

Epidermolysis bullosa (EB) is a rare inherited genetic disease characterized by an abnormal response of the skin and mucosa to mechanical trauma. EB is divided into three major forms: the simplex, the junctional, and the dystrophic. The dystrophic forms of EB (DEB) are accompanied by extensive scarring because of sublamina densa blistering of the skin. The ultrastructural hallmark of the dystrophic forms of EB consist of an aberration in anchoring fibrils, either morphologically abnormal, or in reduced number, or completely absent. After the findings that anchoring fibrils are predominantly made of type VII collagen (COL7), mutation analysis of its gene (COL7A1) has become routinely for diagnosis. Very often DEB is characterized by many extra cutaneous complications. In particular, several renal complications have been reported for DEB in the recessive form, such as IgAN.

Case N. 1

E.B. is a male 22 year old patient diagnosed of recessive dystrophic form of EB genetically confirmed. When he was six years old, he underwent to surgical procedure for correction of hand syndactyly. Skin was removed from tights, the only body part showing no damage or scars from EB. After this procedure, a chronic flogistic phenomenon was evident at tight level. Chronic inflamma-
tion was treated and resolved with high dose 16 mg/die of the leukotriene receptor antagonist montelukast. At the age of 17 blood tests showed severe anaemia (Hb < 8 g/dl and albumin 2.5 g/dl) along with hyposideraemia (5 µg/ml) with normal transferrin, elevated platelet count (731 × 10⁹/µl), prolonged coagulation time and microcytosis. He showed moderate renal failure (creatinine 0.69 mg/dl, creatinine clearance 50-60 ml/min per m² body surface area), proteinuria (2.5 g/24 h) and increased levels of serum γ-globulins (IgG 29,500 g/l, IgA 4,900 g/l, normal IgM and IgE) and inflammatory markers [erythrocyte sedimentation rate (ESR) 93 mm/h, C-reactive protein (CRP) 39.2 mg/dl]. More detailed analysis evidenced the presence of auto-antibody against COL7 and pemphigoid bullous 180 (BP180) antigen. Like many EB subjects, he was hyposomic, with 25-hydroxy-vitamin D deficiency and delayed puberty.

One year later, the patient was admitted for severe vasculitis Henoch-Schönlein purpura-like. He presented abdominal cramps, melena, and haematemesis. Blood test confirmed the early pattern with a more severe thrombocytosis (826 x 10⁹/µl), high ESR (107 mm/h), CRP (112.7 mg/dl) and IgG, IgM and IgA levels. Renal function was still compromised (creatinine 0.61 mg/dl) with proteinuria (30 mg/dl). He was treated with betametasone, 2 mg/bidie, and the intestinal symptoms along with high IgA presence, suggested a concomitant disease, such as celiac disease or gluten sensitivity, and thus a gluten free diet (GFD) was started. Further analyses showed positive anti-gliadin IgG and anti-endomysium. After 5 months of GFD and betametasone treatment, proteinuria was resolved and the general state of the patient was improved. He underwent puberty and hyposomia was resolved. Betametasone was lately reduced to 0.5 mg/bidie.

Case N. 2
R.P. is a 10 year old patient diagnosed of DEB genetically confirmed. He was admitted to the clinical ward for reiterated episodes of haematuria. Blood test showed thrombocytosis (454 x 10⁹/µl), high ESR (107 mm/h), and eosinophil cationic protein (ECP) (24.5 ng/ml). Hyposideraemia (15 µg/ml) was associated with low transferrin (154 ng/ml)and normal ferritin (152 µg/ml). Blood tests also showed severe anaemia (Hb< 8 g/dl and albumin 2.5 g/dl) along with elevated IgG (3824 mg/dl). In addition, he presented proteinuria (50 mg/dl) and compromised renal function. He underwent GFD and low dose betametasone. Moreover, he was also positive for BP180 and COL7 antibodies. After the diet, proteinuria was resolved and Hb returned to normal (12 g/dl).

Discussion
In the present report we showed the beneficial effect of GFD accompanied with low doses of betametasone in two patients with DEB. Epidermolysis bullosa is generally considered a skin disease, however, severe forms of EB such as the dystrophic recessive one, are often characterized by several extracutaneous manifestation, inso-much that it can be considered as a multisystem disorder. DEB has been associated with several complication and in particular renal dysfunction. Very often this generalized form of EB is complicated by low bone mineral density, factor associated with other pathology complications such as anaemia, infection, undernutrition, reduced mobility, short stature, more extensive skin blistering and chronic inflammation. Gastro-intestinal problems in EB are very common with subtype specificity for some of these complications. In particular, it has been reported that the occurrence of diarrhoea, Protein Losing Enteropathy and colitis in the context of EB may derive from secondarily to antigenic exposure in the gut lumen as a result of mucosal fragility. Indeed, in an animal model of EB acquisita, it has been shown that COL7 is expressed in different portions of the gut and that anti-COL7 antibodies induce distinct gastrointestinal tissue damage. In dystrophic patients chronic gut inflammation is likely to be present, since the defective COL7 is present across the intestine, thus we hypothesize that insults originated from food antigens might precipitate extra epithelial manifestation of the disease. In line with this hypothesis a recent report has revealed some histological signs of inflammatory processes in EB paediatric patient experiencing gastrointestinal complication. The Authors hypothesized that these phenomena were attributable to either epithelial adhesion defect or to an autoimmune autoimmune-type process, where the splitting of the basement membrane would expose of normally “hidden” antigenic components inducing autoimmunity. This latter hypothesis is strictly in line with the condition of our first patient since he showed
both high inflammation markers and high plasmonic IgA. Unfortunately, due to the fragile condition of these subjects performing an intestinal biopsy to confirm such hypothesis was hardly possible. However, the introduction of GFD was helpful in ameliorating not only gastrointestinal symptoms, but also the general inflammatory state and renal function. Indeed, patients resolved the proteinuria and reported a reduction in the number of wound not related to mechanical trauma. Moreover, they resolved the nutritional defect, and the first underwent to puberty, improving the hyposomic condition. Gluten free diet has been found very useful in ameliorating intestinal function and proteinuria in IgA-mediated nephrology\textsuperscript{13} and this renal pathology has been reported to occur in EB by many case report type publications\textsuperscript{14,15,16}. Thus, it could be hypothesized that in EB patients the chronic intestinal inflammation may be worsened by gluten and other food additive leading to over production of inflammatory cytokine, such as TNF\textsubscript{α} or interleukins, and with the activation of enteric immune response resulting in an overload of IgA. In this regard recently it has been reported the beneficial effect of two biological drugs in EB patients such as the CD20-targeted monoclonal antibody, rituximab, for the acquired form of EB\textsuperscript{17} and the anti-TNF\textsubscript{α} fusion protein etanercept\textsuperscript{18}. GFD has been shown beneficial also in other inflammatory/immune pathology such as in allergic patients\textsuperscript{19}. It is worth to note that in these allergic patients anaemia associated with high or normal ferritin levels was present, indicating that the dependency from a chronic inflammatory condition. This is very common in EB, indeed anaemia, usually related to blood lost from wounds, is present in almost all patients and usually accompanied by normal ferritin, and low iron. The iron deficiency is often refractory to oral supplement and intravenous infusion is required. This point endorses our hypothesis of a chronic intestinal inflammatory condition, explaining the scarce absorption of iron at intestinal level. Interestingly, a recent publication has revealed that in caeliac paediatric patients iron deficiency anaemia was the most common extra-intestinal symptom along with a high incidence of thrombocytosis\textsuperscript{20}. In our cases, both patients were also treated with low doses of betametasone. Although cortisone has been proposed in the past for the palliative cure of EB\textsuperscript{21,22}, its use nowadays is limited. However, here we have found a general improvement of the wellness of this patient after the introduction in the daily therapy of cortisone. The patients reported a reduction of wound formation not derived from mechanical trauma. Furthermore, the sense of general pain and pruritus was reduced with the return to normal daily activities. In particular, free deambulation was achieved and the use of the wheelchair abandoned. At this point is still not completely clear if such beneficial effect is due to the anti-inflammatory effect of cortisone or to its immunosuppressant activity. However the presence in both patients of anti COL7 antibodies and the inflammation indicate that this pathology might be revised in light of an autoimmune/inflammatory disease.

In conclusion, in this report we showed the beneficial effect of a GFD along with low doses of cortisone. In context of EB we believe that it would be very useful to screen patients for celiac disease or for gluten sensitivity. However, due to the particular condition of this population, intestinal biopsy is often not possible to perform, nonetheless it could be useful to perform HLA typing to establish a possible association. This would result very useful, in particular for young patients that can early beneficiate of a GFD to avoid further organ damage typical of DEB.

References

Improvement of renal function in epidermolysis bullosa patients after gluten free diet: two cases


