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### **Chronic Lupus Erythematosus in Children with C2 Complement Fraction Deficiency**

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#### **Abstract:**

Complement has both beneficial and deleterious roles in the pathogenesis of systemic lupus erythematosus (SLE). On the one hand, patients with SLE present with decreased complement levels and with complement deposition in inflamed tissues, suggestive of a harmful role of complement in the effector phase of the disease. On the other hand, homozygous deficiency of any of the classical pathway proteins is strongly associated with the development of SLE.

The homozygous C2 deficiency is the most common deficits as a fraction of complement associated with lupus. We report two children with chronic lupus erythematosus and deficiency of C2. The mechanisms behind this association and the clinical and immunological particularity are discussed.

#### **Introduction:**

The complement plays important role in the defence of the host against infection and the elimination of immune complexes. Therefore the exploration of the components of the complement system is indicated in cases of repeated infections, auto-immune diseases particularly systemic lupus erythematosus (SLE) or in the glomerulopathies.

The association between complement deficiencies and SLE could be explained by several mechanisms, including impaired clearance of immune complexes and impaired handling of apoptotic cells, aberrant tolerance induction or changes in cytokine regulation.

We report two cases of chronic lupus erythematosus and C2 deficiency in two children.

**Case 1:**

A 10-year old female was followed in the dermatology department for skin lesions, appeared a year earlier, in the form of erythemato- papular eruption affecting the nose and cheeks (Fig. 1), erythematous finely scaly hands and feet (Fig. 2a and 2b). There was a scaly patch of alopecia of the scalp, the direct microscopic examination KOH preparations from hair and scales were negative for fungus.



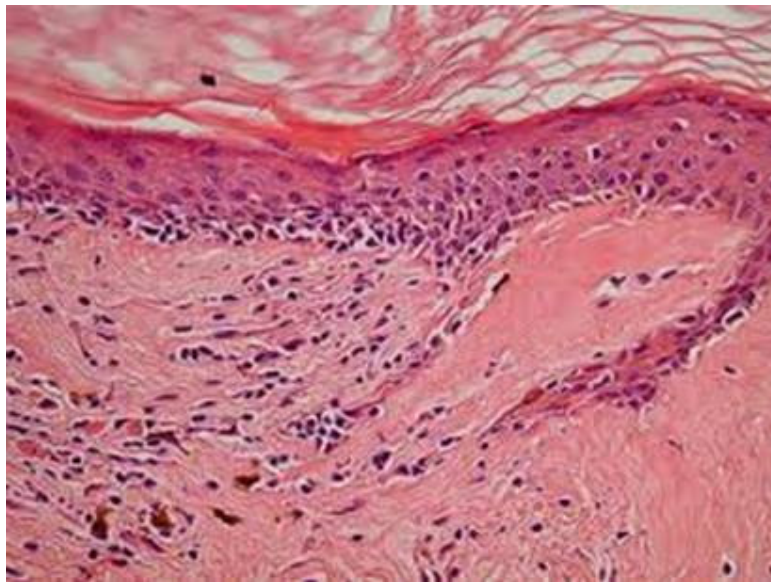
**Fig 1:** Erythemato- papular eruption affecting the nose and cheeks.





**Fig 2a and Fig 2b:** Erythematous finely scaly hands closets.

The histology showed: vacuolar alteration of the basal cell layer, thickening of the basement membrane, hyperkeratosis, atrophy of the epidermis, incontinence of pigment, and inflammatory lymphocytic cell infiltrate in a perivascular, periappendiceal, and subepidermal location that was in favor of chronic discoid lupus erythematosus (Fig 3), and direct immuno-fluorescence showed micro granular IgG, IgM weak fluorescence and C3 at the dermo-epidermal junction.



**Fig 1:** Histopathology showing chronic lupus erythematosus

Laboratory studies showed weakly positive antinuclear antibody at 1 / 160, positive Anti-Ro (SS-A) antibodies. The anti-nDNA antibodies were absent.

Her serum showed homozygous C2 deficiency: Functional C2 activity < 10% (normal 70-115%). C3 =1, 401 g / l (normal: 0,743-1.62), C4= 0,155 g / l (normal: 0,162-0,530).

Her father has a functional C2 to 22%.

No renal or cerebral or pleuropericardial involvement were observed during evolution.

The patient was treated with hydroxychloroquine (Plaquenil ®) at a dose of 4 mg/kg/day and external photoprotection. The evolution was marked by the disappearance of skin lesions.

### Case 2:

A 9-year old female was followed for 2 years in the dermatology department, for scaly erythematous papular plates, affecting the nose and cheekbones. Skin biopsy and direct immunofluorescence showed chronic lupus erythematosus. Laboratory analysis showed weakly positive antinuclear antibody. The Anti-Ro and anti-nDNA antibodies were absent. C3: 1, 070 g / l, C4: 0,176 g / l, CH50 = 0% (normal: 75-138%), functional C2 at 0% and a homozygous C2 deficiency type 1. A rigorous photoprotection was advocated associated with hydroxychloroquine.

### Discussion:

Homozygous deficiency of each of the classical pathway complement components (C1q, C1r, C1s, C4, C2) is associated with an increased susceptibility to SLE [1,2].

The most common homozygous complement deficiency is that of C2, which occurs in 1: 10,000 to 20,000 individuals. Heterozygotes are present in 1 to 2% of the normal Caucasian population. SLE occurs in 10 to 30% of homozygous C2 null individuals [2,3,4]. Of patients with SLE, C2 deficiency accounts for approximately 1% [5]. Heterozygotes do not appear to be at an increased risk for SLE [5].

Inherited deficiencies of C1q and C4 are invariably associated with the development of a severe, lupus-like disease early in life, while C2 deficiency is only weakly associated with a milder form of SLE, an association which has most likely been overestimated [2]. In contrast, whereas deficiency of C3 predisposes to recurrent pyogenic infections and membranoproliferative glomerulonephritis, it is rarely associated with SLE [2].

The association between complement deficiency and SLE appears even more paradoxical: complement deficiency causes SLE, and yet SLE causes activation and consumption of complement. These clinical observations suggest that the early part of the classical pathway plays a key protective role against the development of SLE. A recently described link between the complement system and apoptosis may explain these apparently paradoxical findings [6].

The reasons for the development of SLE in classical pathway deficiencies have been subject to extensive study [2,5,6,7,8]. All findings are compatible with the hypothesis that complement deficiency causes SLE by impairment of the physiological clearance of apoptotic cells by

macrophages. These uncleared apoptotic bodies in turn may provide the source of the autoantigens that drive the autoimmune response of SLE. A reduced ability of macrophages to remove apoptotic cells at sites of inflammation may promote the clearance of these cells by pro-immune antigen-presenting cells, and if the necessary pro-inflammatory cytokine milieu is present, this may drive dendritic cell maturation and initiate an autoimmune response followed by tissue damage and complement activation.

The clinical findings observed in SLE patients with C2 deficiency include early onset, skin lesions resembling discoid lupus, photosensitivity, mild renal, cerebral and pleuropericardial involvement and repeated bacterial or viral infections. Antinuclear antibody titres are usually low and anti-nDNA antibodies are absent. Anti-Ro (SS-A) antibodies, however, have been found in a large proportion (up to 73%) of patients with SLE and C2 deficiency [5,9,10].

In SLE without a complement component deficiency, anti-Ro antibodies are observed in only 20-30% [9,11] and in Sjogren's syndrome in 40-70% [9,12]. A high incidence (62%) of anti-Ro antibodies have also been described in patients with subacute cutaneous lupus erythematosus [13].

Inherited deficiency of C2 was suspected when the C2 protein was low (less than 2 SD below the mean) or low normal (less than 1 SD below the mean), particularly if other components of the classical pathway were within the normal range [14]. Functional C2 activity was then measured in those individuals with this apparently isolated deficiency of C2 or a low normal value. If the functional C2 level was less than 2 SD below the mean, multiple samples stored at intervals during routine clinical follow-up were analyzed retrospectively by both C2 protein and functional assays to exclude acquired changes in C2 levels [14].

The C2 gene is located in the middle of the major histocompatibility complex (MHC) class III region together with the genes for C4 and factor B. Two principal variants of C2 deficiency have been distinguished: type I is characterized by the absence of detectable C2 synthesis, while type II is caused by a selective block of C2 secretion [15].

## Conclusion:

C2 deficiency is associated with many diseases e.g. vasculitis, glomerulonephritis, dermatomyositis, but association with discoid or systemic lupus erythematosus is the most common. Lupus associated with C2 deficiency has clinical and immunological particularity.

Homozygous deficiency in one or several fractions of complement is usually suspected when CH50 was low.

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