

Primary ciliary dyskinesia

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Key words: asthma; atopy; ciliated epithelium; immotile cilia syndrome; primary ciliary dyskinesia; transmission electron microscopy.

• A 14-YEAR-OLD girl with past history of asthma, allergic rhinitis, and conjunctivitis was admitted to the hospital for progressive dyspnea. The physical examination revealed inspiration and expiration wheezing associated with diffuse ronchi and rales.

A case of allergic asthma.

PFT revealed mild flow obstruction not reversible after inhaled salbutamol (200 µg); ABG on room air showed PaO_2 of 66.2 mmHg, $PaCO_2$ of 34.6 mmHg and pH 7.425. The prick test demonstrated strong positivity for house-dust mite and atmospheric pollens (*Parietaria* and *Assenzio*). Tests of sweat and the genetic map for cystic fibrosis were negative. Radiographic examination (chest, HRCT) was not specific.

Light microscope. The microstructure of the mucosa under examination appeared to be within the limits of normality. High-grade enlargement showed the free surface (no mucus) of the covering epithelia to be occupied by cilia regularly distributed.

Transmission electron microscope. With low-grade enlargement, it was found that the cilia were homogeneously distributed and had about the same diameter. However, with strong enlargement, we noticed:

- 1) plasmalemma well structured but thickened in every microvillus
- 2) free space between plasmalemma and axonoma was variable: for some cilia, it was above average for slight edema
- 3) well-developed axonoma; it was possible to distinguish the central microtubules from the pairs of peripheral microtubules, which maintain a regular arrangement in space
- 4) absence of dynein lateral arms and reduction of connection rays and loss of nexina pontes in the subcellular organization of the axonoma.

Primary ciliary dyskinesia (PCD) is a rare, heterogeneous disorder, usually transmitted with a recessive autosomal tract, and characterized by the axonomal anomalies of the respiratory epithelium cilia.

In the diagnostic examination for PCD, electron microscopy represents an important tool, even if it remains difficult to distinguish the congenital ciliary alterations from those following chronic respiratory pathologic states.

According to Rossmann et al. (1), the report of aspecific ciliary damage involving less than 5% of the epithelial cells would suggest an acquired disorder. However, the loss of differentiated epithelial cells and the ultrastructural defects of the ciliary system are much larger in carriers of PCD than in patients with damage deriving from a chronic respiratory pathologic state (2).

We found ciliary ultrastructural damage, both specific (ciliary bodies with loss of axonoma arms) and aspecific. The diversity in specific ciliary ultrastructure among different patients with the same

clinical symptoms is due to the fact that the immotile cilia syndrome is a heterogeneous disease, and the underlying defect may reside in any of a great number of ciliary genes. A commonly observed defect is the absence of the so-called dynein arms; other reported ultrastructural abnormalities include abnormal radial spokes and improperly oriented, absent, or additional microtubule assemblies. In 10–20% of cases, the living cilia are seen to be immotile but the ciliary ultrastructure appears to be quite normal; this probably reflects an underlying defect in membrane pumps or in other proteins not visible in electron micrographs. In our case, the subcellular organization of the axonoma showed the absence of dynein lateral arms, reduction of connection rays, and loss of nexina pontes.

The aspecific aspects, as related to the phlogistic asthmatic situation, could be considered an aggravating factor in the early clinical manifestation of the genetic disorder. Therefore, in addition to an increased incidence of respiratory infections with chronic cough and expectoration of mucopurulent sputum, an asthmatic presentation may be encountered in PCD.

Houtmeyers et al. (3) described the possible modifications of the mucous-ciliary clearance (MCC) caused by drugs used in patients with an insufficient mucous-ciliary transport system. However, the kind of drugs administered to our patient (corticosteroid and β_2 -agonist) during the period preceding the diagnosis did not influence the pathologic situation codified as PCD. In fact, it must be pointed out that the use of a β_2 -agonist is

advisable for young patients with PCD, especially when combined with physical therapy (4).

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C4 deficiency in chronic angioedema

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Key words: angioedema; C4 deficiency.

● HEREDITARY angioedema (HAE) is an autosomal dominant disorder caused by decreased level, or functional deficiency, of the C1 inhibitor protein.

We describe a patient with diminished levels of the C4 and C2 complement components, with episodes of chronic angioedema, and showing a genetic deficiency of C4 protein. The patient was a 46-year-old woman with a 2-year history of episodic angioedema. The parts of the body involved were the eyelids, cheeks, tongue, and upper airway. She also suffered from abdominal attacks with cramp-like pains and vomiting. Skin swellings were very frequent (two or three per month) without apparent cause. There was neither pregnancy nor estrogen administration during these 2 years. The laboratory results were as follows: C4 3.8 mg % (normal range 15–47); C2 <4 mg % (4–24); C3 80 mg % (100–185). All these values had been reproduced at several time points. C1 inhibitor levels and function, C1q, C4bp, AP50, and CH50 were in the normal range, as was IgG, IgM, and IgA. Antinuclear antibodies, rheumatoid factor, cryoglobulins, HB_sAg, Anti-HB_c, Anti-HCV, and immunocomplexes were negative. The complement profile in her family showed normal values in her mother and brother, while C4 was low in her other two brothers and in her three children (9.6–13.4), one of whom had had several episodes of angioedema during puberty. C3 was slightly diminished in her sister

A case of partial genetic deficiency.

and two of her children (82–92). C1 inhibitor, C2, and the functional activity of C1 inhibitor were normal in all her family members. Data from the patient's father were not available because he was dead. The patient was treated with tranexamic acid 500 mg/h, and remained almost asymptomatic.

Our patient had a clinical disorder with characteristics of HAE, including a low C4 and a good response to tranexamic acid. However, the normal levels and function of C1 inhibitor ruled out this disease. A partial genetic deficiency of C4 was observed in several members of her family. In addition, the patient had a low level of C2, and a slight reduction in C3. The latter was also found in some members of her family. These facts suggest an associated deficiency in C4 and C2, which could be explained by the close location of both genes at chromosome 6. The reduction in C3, however, cannot be ascribed to the same reason, because it is placed at chromosome 19. Although a reduction in levels of these complement proteins might be due to activation of the classic pathway, we did not find any evidence of such a process. The patient had neither clinical symptoms nor analytic markers of diseases, such as dermatomyositis and vasculitis, associated with C4 or C2 deficiency.

Recently, HAE with normal C1 inhibitor and its activity has been described in women (1). For this disorder, the authors proposed the term "hereditary angioedema type 3". The presence of diminished C4, and the absence of symptoms depending on high estrogen levels (pregnancy, oral contraceptives, and hormone replacement therapy) exclude such a disease. Llatser & Guillaumet (2) have described a family with C4 and C2 deficiency, and two brothers affected by angioedema.