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EDITORIAL

Bronchiolitis obliterans in children: A ghostly journey to the origin

Bronchiolitis obliterans (BO) is a rare fibrosing form of chronic obstructive lung disease after lung transplantation, smoke inhalation or after a severe viral insult to the lower respiratory tract, resulting in narrowing and sometimes complete obliteration of the small airways.¹

BO in children mostly follows a severe viral lower respiratory tract infection. Several studies have suggested that the disease is more common in the southern hemisphere; people from Asian descent appear to be especially susceptible. Recently the HLA haplotype DR8-DQB1.0302, an allele highly represented in the Amerindian population, was associated with an increased incidence of BO, providing a possible explanation for the high frequency in South American countries.²

Adenovirus is the leading infectious cause of BO worldwide³; however, isolated cases after RSV, measles, influenza, parainfluenza and *Mycoplasma pneumoniae* are reported.

Severe respiratory compromise during the acute adenovirus pneumonia predisposes to an evolution to BO.^{4,5}

A rare but severe and often progressive form of BO was observed as a complication of the Stevens–Johnson syndrome.⁶

A clinical diagnosis is made when after a severe viral bronchiolitis, or sometimes pneumonia with respiratory insufficiency, tachypnoea, wheezing and hypoxaemia persists for at least 60 days. Symptoms may wax and wane over weeks to months. Physical examination reveals crackles and wheeze by chest auscultation, a barrel chest, tachypnoea and sometimes hypoxaemia.

The chest X-ray shows hyperinflation, bilateral interstitial prominence, atelectasis and consolidations. HRCT thorax is characterised by mosaic perfusion, vascular attenuation and central bronchiectasis. Lung function reveals dramatic hyperinflation: increased residual volume (RV), thoracic gas volume (TGV) and a pronounced obstructive flow volume curve: decreased FEV1, FEV1/FVC and mid-expiratory flows (FEF25–75, FEF50).

From a pathological point of view BO is characterised by partial or complete obstruction of the lumens of terminal and respiratory bronchioles by inflammatory and fibrous tissue.¹ Two major histopathological types are reported, which can be part of a continuum.

The first rare type is characterised by inflammatory and granulation tissues obstructing the small airways, extending into the alveoli causing atelectasis and alveolar consolidation. This type is known as BO with organising pneumonia or as it is more usually named now, cryptogenic organising pneumonia. The second, much more common type known as constrictive bronchiolitis is characterised by inflammation and fibrosis of the wall of bronchioles leading to a fixed obstruction and sometimes occlusion of the airway.⁷ The latter is found in 97% of childhood BO.

BAL fluid (BALF) of BO patients contains increased levels of interleukins (IL-6, IL-8), Tumour necrosis factor- α , and neutrophils as hallmarks of ongoing inflammation.⁸ Increased levels of CD8+ T-cells suggest an impact of T-lymphocyte driven inflammation.⁹

The paper of Mallol et al. in the current issue of *Allergologia et Immunopathologia*¹⁰ shows that in 21 children with BO, oxidants such as 8-isoprostane derived from triglycerides and carbonyls from proteins are obviously increased in BAL fluid, whereas anti-oxidants such as catalase and glutathione peroxidase are normal or increased respectively.

Neutrophils, eosinophils and alveolar macrophages, recruited by a toxic respiratory impact (viral infection, smoke inhalation, etc) are notorious producers of Reactive Oxygen species (ROS), but also epithelial and endothelial cells can provide ROS. ROS enhances inflammation and tissue damage. ROS (superoxide and hydrogen peroxide) reacts with a number of substrates to generate harmful radicals. Increased ROS production is reported in patients with asthma¹¹ and CF.¹²

The paper of Mallol et al.¹⁰ reports in BO, a pathologic setting of patients with ongoing respiratory inflammation driven by interleukins and TNF- α attracting inflammatory cells, increased ROS and c.q. oxidants.

The values of the antioxidants are somewhat unequivocal; an increase in glutathione oxidase could counteract the increase in oxidants, whereas the lack of increase in catalase in an inflammatory region with increased oxidants can enhance inflammation. The study did not find any correlation between oxidant concentration and lung function deficit. Oxidants were, however, measured in BALF without any estimation of the absolute concentration, facilitating comparison between samples. The concentration measured,

will be dependent on the degree of dilution, which will be very different between BALF samples. Comparing urea or albumin concentration in serum and BALF could determine a dilution factor giving the opportunity to calculate the relative concentration of the different oxidants and anti-oxidants which facilitates comparison between different samples, probably leading to a greater chance on correlation with lung function parameters.¹³ Moreover lung function deficit could have been the result of the early devastating infectious process, resulting in a more pronounced fibrosis, with less chronic inflammation and therefore lower oxidant values.

From a methodological point of view the authors admit that there are some weaknesses. Unfortunately the study lacks a real control group and relies for the normal values on scarce data, for which the methods of measurement are not mentioned. The demographic data of the study group are minimal: what was the median age at the primary infection, the median duration of the disease, were children with a progressive or a stable disease included? Possible confounders were disregarded: the effect of passive smoking or living in a polluted agglomeration.

Nevertheless the authors put forward a challenging statement, pointing at oxidant/anti-oxidant imbalance in the pathology of BO in children and raised a lot of probable ideas for further research.

Is there any difference in oxidant/antioxidant imbalance defined by the activity of the disease, stable or progressive disease, fibrotic or inflammatory forms?

Why are some children developing BO after an adenovirus infection? Are there genetic backgrounds? Polymorphisms in TNF- α or glutathione-S-transferase M1 have been reported¹⁴ to give a different risk for asthma in oxidant environments.

Treatment options are in general supportive: avoiding passive smoking and inhalation of irritants which could increase the oxidative stress, airway clearance techniques and oxygen for children with hypoxaemia. In children with reversible bronchoconstriction a therapeutic trial with inhaled bronchodilators, corticosteroids and even systemic steroids is recommended.

As BO is an inflammatory disease the outcome of treatment with systemic corticosteroids is unknown. If corticosteroid treatment is given it should be started early, before fibrosis has developed.

Treatment with azithromycin, a macrolide has proven to be effective in diffuse panbronchiolitis, cystic fibrosis and also in bronchiolitis obliterans syndrome (BOS) after lung or bone marrow transplantation. In the latter disease Azithromycin was proven to reduce airway neutrophilia and IL-8 mRNA.¹⁵ Although not studied in post-infectious BO, a therapeutic trial with azithromycin is warranted in an inflammatory mediated form of disease. In cases of respiratory insufficiency transplantation could be considered, although this option is taken in BOS, no reports of transplantation in post-infectious BO are published!

Relying on the increased oxidants in BO, oxygen scavengers could be an experimental anti-inflammatory treatment option. Papers on the use of N-acetylcysteine as an oxygen scavenger are, however, scarce and unequivocal.¹⁶

The paper of Mallol et al.¹⁰ reports an increased level of ROS in children with BO. As usual in science their

findings lead to a lot of unanswered questions, inviting to further research.

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