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***Corresponding Author**
Ana Belen Ariza Jimenez
E-mail
micodemas@hotmail.com
Contact
+34666154496

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Pulmonary Hypertension in Children with Down Syndrome without cardiopathy

Ana Belen Ariza Jimenez[1]*, Estela Perez Ruiz[1,2], Pilar Caro Aguilera[1,2], Francisco Javier Perez Frias[1,3]

[1]Pediatrics. Malaga´s Children Hospital. Avda Arroyo de los Angeles s/n 29010. Malaga. Spain
[2]Pediatric Pulmonology Unit. Avda Arroyo de los Angeles s/n 29010. Malaga. Spain
[3]Malaga´s University. Avda. Cervantes 2. 29071. Malaga. Spain

Abstract

Patients with Down syndrome have an increased risk for suffering from pulmonary hypertension, despite not having heart disease, but pathophysiology is rarely known. Those mechanisms justify a low response to nitric oxide, so we explain pathophysiology to explain this response and give other choices of treatments in those cases.

Sr Editor,

Down's syndrome is related to children's interstitial lung disease or diffuse disorders of development, which has an increased risk for suffering from pulmonary hypertension, despite not having heart disease, with an incidence of 1.2% versus 0.6% from the rest of the population [1, 2]. Already in a study published in the "New England Journal Medicine" in 1982, 85% of the cases with Down syndrome showed early vascular lesions and rapid evolution related to pulmonary hypoplasia, both in presence and in the absence of congenital heart disease, thus aggravating existing pulmonary hypertension [3].

Furthermore, related to that, it was demonstrated a different development in children with Down Syndrome, not described in other situations. They show a compensatory polyalveolar acini until 3 months of age, alveoli and dilated ducts associated with a double capillary network at 4 months of age, and a small lung volume for the age in children under 6 months [4].

Their predisposition to pulmonary hypertension in absence of heart disease is based on molecular and vascular defects, which results in diffuse accumulation of mesenchyme into the alveolar interstitium, acinar dysplasia due to late growth of canaliculi and early saccular phase, alveolar dysplasia with malposition of pulmonary veins, small arteries, hypertrophy of middle layer of the arteries and arterioles, decrease in capillary density and abnormalities in lobular development [5].

Cooney et al. found an increase in cell apoptosis and deficiency of elastic fibers in the alveolar wall, which suppose a decline in alveolar área (4.6 alveoli/acinus) with interstitial emphysema, thin alveolar septa, and elongated alveoli and alveolar ducts [6]. Schloo et al. described pulmonary hypoplasia, a decrease in acinar complexity, multiplication, and alveolar radius due to abnormalities in mechanisms of growth [7].

Inhibition of growth receptors and angiogenic growth factors resulted in hypoventilation, tissue damage, increase of resistance and disruption of capillary development required for the development and maduration of the alveoli [8,9]. A mutation of bone morphogenetic protein receptor type II gene, that control growth factors and kinases function, has been described, which suppose intimal hyperplasia, proliferation of endothelial cells and smooth muscle of pulmonary arteries, higher production of thrombi and increased blood pressure [10-12]. All of these produces a smaller lung determined by genetic factors, oxygen surface tension, nutrition, hormones and growth factors [13].

There is an increase of oxidative stress, with reduction and inactivation of oxide nitric, an increase in endothelial proteins (nitric oxide synthase endothelial, fetal hepatic kinase, hypoxia inducible factor 1 alpha subunit, and activin like kinase), vascular oxygen and free radicals, and a decrease in vasoactive substances (L-Arginine, prostacyclin synthase) and vasodilation response, which increase pulmonary hypertension [13].

Furthermore, the increase of endothelial proteins in alveoli´s capilars are related to dysplasia and malformations of pulmonary veins [14]. The response to nitric oxide in Down syndrome is 21% lower in the presence of pulmonary hypertension, due to vascular alterations and a greater amount of oxygen [15]. Currently, based on the exposed findings, some possible treatments for the improvement of respiratory symptoms and pulmonary hypertension in Down syndrome could be prostaglandin analogs, phosphodiesterase 5 inhibitors and bosentan [4,12].

Conflict of Interest

None of the authors have any conflict of interest and none of us have received any grant, economic support or contribution for writing it.

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