Respiratory syncytial virus bronchiolitis and hypertransaminasemia

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SUMMARY

Bronchiolitis is the most common disease of the lower respiratory tract occurring in children during their first year of life, becoming the most frequent cause of hospitalisation (with a peak of 2 month-old newborns). It is estimated that at least 70% of bronchiolitis cases, especially in their severe forms, are caused by respiratory syncytial virus (RSV); other causes include Metapneumovirus, Parainfluenza virus, Influenza virus, Rhinovirus, Bocavirus and Adenovirus. RSV is a linear single-stranded RNA virus belonging to the Paramyxoviridae family. RSV has a seasonal pattern, which mainly ranges from October to May, its peak of isolation is shown in February; a seasonal break is observed during months with higher temperatures and lower humidity [1]. It is extremely contagious; the virus is transmitted through saliva droplets in the air, and through contact with contaminated objects and surfaces. Acquired immunity, after an RSV infection, is incomplete and short-lived and this results in frequent reinfection throughout life. As found in literature, almost all children, within their first two years of life, get in contact with RSV, but only 0.5-2% of cases with contracted RSV infection, require hospitalisation. Factors related to an increased risk of hospitalisation include: family history of asthma and/or atopy, parental smoking, lack of breastfeeding, low birth weight, prematurity, birth during the epidemic period, birth by caesarean section, low socio-economic conditions, domestic pollution, environmental overcrowding, coexistence of associated comorbidities such as congenital heart disease, Down syndrome, neuromuscular and chronic respiratory diseases, and the state of immunosuppression.

Bronchiolitis may present a wide range of clinical symptoms: from mild respiratory symptoms to severe respiratory failure. Clinical-anamnes-
tic criteria that may help diagnose bronchiolitis, include: the onset of rhinorrhea and symptoms involving the upper airways during an epidem-
ic period, associated by crackling sounds and/or bronchospasms that may be heard by auscul-
tation of the chest, use of accessory respiratory muscles (intercostal retractions or sub-costal and jugular), increased respiratory rate for age, fever (present in about 30% of cases), low levels of oxygenation saturation, and feeding problems. The criteria for hospitalisation include: respiratory distress, apnea, need for O₂ therapy (SpO₂ <90-92%), dehydration or problems feeding, presence of comorbidities, and poor family compliance.

Diagnosis is primarily based on the interpretation of the medical case history and physical examination; the etiological diagnosis may be defined by isolation of the virus by culture, or through research of viral antigens in epithelial cells of nasopharyngeal secretions. Treatment is essentially supportive and aims to ensure supply/adequate hydration, and an optimum degree of oxygenation; if necessary, infusion therapy and oxygen therapy shall be administered [2, 3].

Recently, extrapulmonary manifestations associated with RSV infections, including liver involvement, have also been described in literature [4]. The evaluation of a patient with elevated amino-transferase levels should include a first line investigation: blood count, GGT, alkaline phosphatase, total and direct bilirubin, coagulation, total protein and electrophoretic protein pattern, glycae-
mia and viral infections screening for major and minor hepatotropic viruses such as HAV, HBV, HCV, EBV, CMV.

Cases with clinical-anamnestic indications should undergo a second level investigation for ceruloplasminemia and cupremia, ANA, ASMA, LKM1, alpha 1-antitrypsin, liver ultrasound, sweat testing and a third level investigation: HCV RNA, HBV DNA, genetic/metabolic screening including blood-gas analysis, uric acid, lactic acid, ammonia, aminoacidemia, urine organic acids, acylcarnitines dosing, very long chain fatty acids dosing; diagnostic imaging with MRI, colangi-geo-RM, CT, ERCP and fecal elastase steatocrito; liver biopsy [5, 6]. The purpose of this paper is to present three cases of RSV bronchiolitis in children with increased transient aminotransferase level.

### CASE REPORTS

The cases described, concern three male children (1st case 2.5-year-old, 2nd case 4-month-old, 3rd case 1.5-year-month-old), hospitalized for mild to moderate RSV bronchiolitis. While positive family history for asthma and/or atopy, there was no history of prematurity, nor were there any associated comorbidities. On examination, the three children appeared rosy, with preserved skin tur-
gor, and a refill time of less than 2 seconds. Chest auscultations revealed some crackling sounds and wheezing, as well as mild and inconstant subcostal retractions; SpO₂ 95% in room air; RR increased slightly due to their age. According to the guidelines, all three children were treated with irrigation and aspiration of the upper airways. Because there was no fever, antipyretics were not administered. During the hospital stay, all three children showed no signs of respiratory distress, and were fed in a more or less regular way; there was no need to give oxygen therapy, nor to initiate infusion ther-

### DISCUSSION

The first case of possible extrapulmonary involvement in RSV infection, was indicated in 1979,
when Griffin et al. described a fatal case of Reye Syndrome, affected by a severe form of RSV bronchiolitis. The virus was identified through immunofluorescence of the epithelium cells present in the bronchioles. Contextually, metabolic and toxic cofactors, were also supposed, as e.g. the utilization of salycilates in hepatic failure pathogenesis of the patient [7].

In recent years, many extrapulmonary manifestations have been caused by RSV, including cardiovascular failure associated with myocardial damage (35-54%), cardiac arrhythmias such as supraventricular tachycardias and ventricular tachycardias, central apneas (16-21%), generalized seizures and focal, hyponatremia (33%) associated with an increase of the secretion of antidiuretic hormone, and elevated aminotransferase and hepatitis (46-49%) [4]. One such case which reports the correlation with RSV, was demonstrated by means of a liver biopsy and a culture of RSV on the sample biopsy [8]. In the three cases, the transitional and isolated transaminase increase was early, in accordance with what described in the literature; two cases showed this at the time of admission, and the other case showed it on the third day of hospitalization. Similarly, the GGT increased quickly, and stayed high alongside the hypertransaminasemia. The other routine blood tests, including the liver function tests, gave normal results. Once the elevated aminotransferase levels were confirmed, it was decided to start a diagnostic laboratory and instrumental investigation that ruled out an infectious, metabolic and autoimmune cause of hypertransaminasemia. Iatrogenic origin was also excluded because acetaminophen was not administered in any of the three cases; it is known that such a drug, for routine use in children, can cause a transient increase of transaminases [9]. From the point of view of infectious diseases, the only data found was the positive result from the nasal swab carried out at the start. The monitoring of serum transaminases and GGT value, performed during the days of hospitalisation, and later in a protected discharge regime, showed a progressive but gradual reduction to normalization; this occurred approximately one month after the initial feedback. Such a trend was detected to be in line with the GGT. Also, it was found that hypertransaminasemia was not associated with severe respiratory cases, but with a mild to moderate bronchiolitis framework that does not consequentially require oxygen therapy. This contradicts most of what is reported in literature; usually, the finding of elevated aminotransferase levels, or hepatitis, results in acute bronchiolitis cases from moderate to severe that sometimes requires ventilatory support [10, 11].

CONCLUSIONS

In the case reports, described in literature, peak transaminase levels were found to occur between the second and the fourth day of hospitalisation, and respiratory disease was found to be more severe in children with elevated transaminase levels; in some cases, ventilator assistance was required.

From the etiopathogenetic point of view, besides an haematogenous spread and direct invasion of the liver by RSV, it was recently hypothesized that the CD8 cytotoxic T lymphocytes have a role in pathogenesis, but their exact role is not yet clear. Most of the extrapulmonary effects appear to be the final result of the release of inflammatory mediators such as cytokines and chemokines, triggered just by an infection of the respiratory tract by RSV. The antiviral immune response, and cell-mediated infection by RSV, is orchestrated mainly by respiratory epithelial cells infected by RSV, and by alveolar macrophages. Cytokine storm T-helper type 1 (IFNγ, IL-2, IL-12), cytokines T helper type-2 (IL-4, IL-5, IL-6, IL-10), antiviral interferons (IFN, IFNβ) and chemokines (C, CC, CXC and CX3C subgroups), released by epithelial cells of the respiratory tract, can regulate the immune profile and the reaction in peripheral tissues. The host genetic factors can further affect the increased immune response in extrapulmonary sites [12].

REFERENCES


