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**Severe pulmonary hypertension mimicking pulmonary veno-occlusive disease as presenting feature of Non Ketotic Hyperglicinaemia**

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Introduction: Nonketotic hyperglycinaemia (NKH) is an autosomal recessive disorder characterized by defective glycine degradation by the mitochondrial glycine cleavage system (GCS), with early or "late-onset" (atypical NKH) neurologic symptoms. The association of Pulmonary Hypertension (PH) to this disease is uncommon, and the characterization of this PH and its response to vasodilator treatment has not yet been reported. We report five infants in which severe PH was the main clinical manifestation of NKH.
Methods: Retrospective study of clinical records, echocardiograms, cardiac catheterization, enzymatic studies (liver biopsy), and necropsy findings from five infants diagnosed with PH and NKH.
Results: There was history of parental consanguinity in one of the families (three affected siblings) and of a previous son deceased with diagnosis of PH in another. Median age at diagnosis was 3 months (2-4 months). Presenting symptoms: respiratory distress (n=4), cyanosis (n=4), poor feeding/vomiting (n=4), associated intercurrent infection (n=4). Subsequently, all developed severe respiratory and right heart failure requiring mechanical ventilation and iv inotropes. Only one showed seizures/neurologic impairment. Chest X ray at admission: normal-sized heart (n=5), sparse perihiliar alveolo-interstitial infiltrates (n=4). Echocardiography: suprasystemic pulmonary pressure and right-left shunting through foramen ovale (n=5). Chest angio-CT (n=3): diffuse ground glass pattern suggestive of pulmonary veno-occlusive disease. Cardiac catheterization (n=2): normal PCW, median pulmonary/systemic pressure ratio 95%, and pulmonary/systemic resistance ratio 0,8). Median blood and CSF levels of glycine were 1174.4 mcmol/L (649.3-1241.4) and 18.8 mcmol/L (10.9-101.2), respectively, and median GCS levels in liver tissue was 4.3 µkat/Kg prot (0-7.7). Follow-up (median 27 days; range 8-48): after vasodilatory treatments (nitric oxide, sildenafil, bosentan, treprostinil, iloprost, epoprostenol), either alone or in combination, all developed pulmonary edema/haemorrhage, dying of hypoxemic respiratory failure and cardiogenic shock. Necropsy confirmed the diagnosis and CNS involvement, but didn´t found anomalies in lung capillary or venous vessels, and only mild/moderate hypertrophy of the muscular layer of intraacinar arterioles.
Conclusions: 1) NKH should be ruled out in any infant with PH, even without neurologic symptoms. 2) Vasodilator treatment of PH in NKH induce untreatable pulmonary edema 3) Early diagnosis of NKH-PH could avoid aggressive treatment and allow prenatal diagnosis in subsequent pregnancies.