G37 Neurofibromatosis Type 1 Associated With Hydrocephalus and Acute Cardiac Failure: A Fatal Case

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The goal of this presentation is to contribute to the diagnosis of the cause of death in a case of intracranial hypertension due to hydrocephalus and associated acute cardiac failure.

This presentation will impact the forensic community and/or humanity by providing a rare case of tetraventricular hydrocephalus associated with intracranial hypertension and acute cardiac failure in a young boy affected by neurofibromatosis type 1. Disturbance in central sympathetic control resulting in sympathetic hyperactivity has been suggested to be the most likely mechanism responsible for the cardiovascular complications during acute ICH. It would be an important contribute to the scientific community for the diagnosis of the cause of death in ICH.

Test: Neurofibromatosis type 1, also known as von Recklinghausen's disease, is an autosomal dominant genetic disorder, with an extremely wide range of manifestations, and a multisystemic involvement; its incidence is of 1 in 3.500 newborns, and its prevalence of 1 in 4.500 newborns, this makes it one of the most common inheritated diseases. It is caused by a mutation of the NF1 gene, located on the chromosome 17, whose product, the neurofibromin, is a GAPprotein which functions as a negative growth regulator, and is thought to be a tumor suppressor. NF1 is clinically characterized by its cutaneous manifestations, café au lait spots, axillary and inguinal freckling, Lish nodules, and multiple neurofibromas with a variable clinical expression, even in the affected members of the same family. The complications of this disease are numerous and can often be fatal. One severe complication is represented by the development of malignant tumors. The less known vascular lesions, in particular in the arterial tree, may also represent a potentially important complication of NF1, in fact they may be the cause, for example, of hypertension, aortic coarctation, cerebral and visceral infarcts, haemorrhage resulting from aneurysms rupture, etc. Moreover, also cardiovascular abnormalities may occur in NF1, in particular cardiovascular malformations (2.3% of patients) such as pulmonary stenosis, aortic coarctation, etc., hypertrophic cardiomyopathy, and other miscellaneous cardiac abnormalities (such as intracardiac tumors, mitral valve prolapse, aortic dilatation, etc.). Other severe complications are hydrocephalus, and osseous dysplasia, which causes severe scoliosis.

We have seen that patients with NF1 have an increased risk for a variety of cardiovascular disorders (vasculopathy, hypertension, congenital heart defect, etc.), but we want to underline that, in some cases, they are the direct complications of NF1 itself that may induce fatal cardiac disorders.

Case Report: A 12-year-old white male, affected by neurofibromatosis type 1 was admitted to our University Hospital with the suspected diagnosis of meningitis. He was diagnosed as having NF1 at the age of 4-years-old, on the basis of the clinical manifestations. His mother was also affected by NF1. The family history was negative for cardiovascular disease. On physical examination upon admission he measured 155 cm in height, and 48 Kg in weight. He presented dysmorphic features including coarse face with frontal bossing, flat nasal bridge, large nose with anteverted nostrils, large lips, prominent midface, numerous café au lait spots (> 1.5 cm) over the body, axillary and inguinal freckling, and multiple dermal and nodular neurofibromas over the trunk and limbs. Moreover he presented macrocephalia (head circumference 58,5 cm), neck stiffness, headache, and he had a temperature of 38°C with vomit for three days. On neurological examination the patient appeared conscious, but sleepy. The remaining physical examination was otherwise unremarkable. The laboratory analysis excluded signs of inflammation.

An urgent CT cranium revealed a tetraventricular hydrocephalus. In the meantime the clinical conditions got worse: the child presented a violent headache, agitation, cyanosis. So he underwent surgery for an emergency ventriculo-peritoneal shunt, 20 cc of clear fluid were drained, but during the operation he had a bradycardia, wich progressed to cardiac arrest, and then he died for a cardiocirculatory arrest. Death was attributed to acute cardiac arrest during intracranial hypertension resulting from tetraventricular hydrocephalus.

A complete autopsy was performed. External examination confirmed the clinically noted features of NF1. I nternal examination of the cranium revealed an edematous brain, which measured gm 1900 (normal 1400 gm) in weight, with tetraventricular hydrocephalus, a glioma of the left optic nerve, and vasal congestion. Both lungs were heavy and reddish (right 350 g, normal 210, left 300 g, normal 190). The heart weighed 140 g (124 norm), and was in appearance normal in all respects. The epicardial coronary arteries arose normally in a right dominance manner. The autopsy examination was otherwise normal. Microscopic sections of the brain showed a marked edema, cribrosis, little intraparenchymatous haemorrhages, vasal congestion. In the lung it was found edema, acute emphysema, acute stasis, endoalveolar haemorrhages, areas of fibrosis, while in the heart numerous foci of contraction band necrosis, acute stasis, and areas of disarray were found.

The cardiac histological findings require a careful investigation and an adequate interpretation. Contraction band necrosis is a specific morpho-functional entity. Histologically, this form of necrosis is

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characterised by irreversible hypercontraction of the myocell, extremely short sarcomeres, with markedly thickened Z-lines, paradiscal lesion which progresses to a breakdown of the whole contractile apparatus. This breakdown varies from irregular, pathological and eosinophilic cross-bands, consisting of segments hypercontracted or coagulated sarcomeres, to a total disruption of myofibrils, the hole cell assuming a granular aspect without visible clear-cut pathological bands. CBN is observed in many human pathologies, it is not an ischemic change, but the expression of cathecolamine toxicity, as confirmed by experimental intravenous cathecolamine infusion, and by the equivalent human cases with pheochromocytoma. The excess of cathecolamines produces cardiotoxicity through two mechanisms: a) a direct cardiotoxicity, due to the binding of cathecolamines to adrenoceptors; b) an indirect cardiotoxicity, due to the formation, during the metabolisation of the cathecolamines, of highly toxic substances such as aminochromes (adrenochrome) and free radicals, which damage different types of heart membranes, causing intracellular Ca^{2+} overload and myocardial cell damage. The finding of CBN, even if microfocal, could be an important histological signal for interpreting the cause of death and the natural history of a disease in any single patient. It may represent a sign of adrenergic stress linked with malignant arrhythmia/ventricular fibrillation.

Now it only remains to clarify which has been the cause of such cathecolamine surge. The obstructive hydrocephalus related to NF1, generally results from a periaqueductal gliosis which may cause the stenosis of Sylvius's aqueduct, or the blockage of the IV ventricle, resulting in the block of the draining of the cerebro-spinal fluid, the hyperdistension of the upper ventricular cavities, and the increase of the intracranial pressure. In literature there is evidence of myocardial injury following acute intracranial hypertension. It is well established that traumatic head injury with intracranial hypertension (ICH) initiates a cascade of physiological but deleterious events that result in haemodynamic perturbations, electrocardiographic abnormalities. Recent clinical and experimental studies have demonstrated that the pressor and dynamic response of the heart to head injury with acute ICH is mediated by cathecolamine surge, which represents a stress response, mediated by medullary vasomotor centers, triggered by the increased circulatory needs consequent to the decreased cerebral perfusion that follows the sudden ICH. The transient hyperdynamic response of the heart following the excessive sympathetic nervous activation is short-lived and gives way to cardiovascular collapse. In failed hearts, there is histologic evidence of focal myocardial damage that is characteristic of cathecolamine-mediated cardiac necrosis.

The patients affected by NF1 have a reduced lifetime expectancy, because of an increased risk for a variety of fatal disorders, which may be the direct complications related to NF1, but also diseases due to the complications itselves. In the case we report, the obstructive hydrocephalus related to NF1 causes an acute ICH resulting in central sympathetic hyperactivity, that is responsible for the cardiovascular complications during acute ICH.

Neurofibromatosis 1, Hydrocephalus, Sympathetic Hyperactivity

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