

EXPRESSION OF C-FOS PROTO-ONCOGENE IN MEDULLA OBLONGATA IN SUDDEN INFANT DEATH SYNDROME

Authors: Anna Maria Lavezzi, Luigi Matturri - Institute of Pathology, University of Milan, Italy

ABSTRACT - In the present study we investigated the expression of c-fos proto-oncogene, a marker of activated neurons particularly by hypoxia, in the medulla oblongata nuclei involved in breathing after birth, with special reference to Sudden Infant Death Syndrome (SIDS). We utilize the immunohistochemical labeling of corresponding c-fos protein as a tool to identify activated neuronal cells. The study was performed on brainstems of 22 SIDS victims, 13 males and 9 females aged between 1 week and 47 weeks (mean age at death: 17 weeks), and 11 cases as controls, 3 males and 8 females of similar age (mean age at death: 19 weeks), not victims of SIDS and with a well established cause of death. Eight of them died without evidence of chronic hypoxia and 3 with severe pulmonary hypoplasia.

The brainstems were cut according to the protocol usually followed at our Institute and available at the website <http://users.unimi.it/~patol/sids.html>. All the nuclei of the medulla oblongata (in particular: hypoglossus, dorsal vagal motor, tractus solitarii, ambiguus, arcuate and inferior olive nuclei) were examined for c-fos immunoreactivity.

In the control group the immunohistochemical labelling of c-fos protein was generally negative or very low with small number of weakly-stained cells per section with variable localization. Only in a control case died of severe hypoxia, we observed discrete c-fos neuronal positivity in the dorsal motor nucleus of the vagal nerve (DMV).

In the medulla oblongata of SIDS victims there was a substantial increase of c-fos-expression. In fact, in 13 of the 22 cases (60%) we observed positive neurons with strong staining assembled in the DMV bilaterally. The c-fos positive cells were consistently found throughout the rostral-intermediate extent of this nucleus. On the contrary, in the caudal sections of DMV the immunohistochemical staining was negative or limited to low cell percentages.

These data are in agreement with several studies showing that DMV contains different neurochemical subpopulations with distinct physiological roles. It is well established that the caudal region of the DMV is involved in vagal reflexes controlling gastric motility. In the rostral-intermediate levels are instead located motoneurons with respiratory-related activity.

A not-significant scattered distribution of few c-fos-stained neurons was also present in some cases, independently to DMV positivity, in the inferior olive. Although the functioning of c-fos gene still remains poorly understood, the increase of fos-immunoreactivity observed in SIDS suggests that the neurons of the DMV involved in the breathing regulation are able to give an intense and immediate ventilatory response to hypoxia. So our results support the respiratory theory, one of the most credited current hypotheses to explain the pathogenesis of SIDS.

SIDS "GRAY ZONE" DISCLOSED ONLY BY A SERIAL SECTIONS STUDY OF THE BRAINSTEM AND CARDIAC CONDUCTION SYSTEM

Authors: Luigi Matturri, MD; Giulia Ottaviani, MD; Simone G Ramos, MD; Lino Rossi, MD - Institute of Pathology, University of Milan, Italy

ABSTRACT - The SIDS "gray zone" or borderline cases are defined as those cases in which it is difficult to establish if the pathological findings has been sufficiently severe to have caused the death. The complete exam of the brainstem and cardiac conduction system on serial sections in over 100 cases of SIDS, has disclosed 5 SIDS cases in which only our further investigations on the brainstem on serial sections could uncover important anatomo-pathological findings likely representing the morphological substrates for a sudden reflexogenic death. We report a case of discrete T-lymphocytic leptomeningitis of the ventral medullary surface, in a 4-month old female infant dying suddenly and unexpectedly. This infiltrate alone would probably not account for sudden death, but could have had a triggering role. A toxoplasma encephalitis involving the ambiguus nucleus was found in a 1-month-old male infant dying suddenly and unexpectedly. In a 3-month-old boy a tractus solitarius encephalitis was found, not clearly lethal in nature. These three cases are consistent with the triple-risk model of SIDS, an hypothesis consisting of underlying biological vulnerability to exogenous stressors or triggering factors in a critical developmental period. Further studies on triggering factors and related mechanisms will lead to a better understanding of complex interactions involved in the pathophysiology of SIDS. The herein presented case seems to usefully contribute to orient researches in this field. We report an unusual case of benign hemangioendothelioma bilaterally arising from the area postrema invading the medulla oblongata in a 4-month-old male infant dying suddenly and unexpectedly. Post mortem examination was requested with a clinical suspect of SIDS that was confirmed after a complete routine autopsy. However, an accurate investigation of brainstem on serial sections performed in our institution showed the presence of an hemangioendothelioma. In a SIDS victim a complete exam of the cardiac conduction system on serial sections showed the presence of a Purkinje cell tumor. Necroscopy studies of sudden infant death should always include an accurate histological examination of brainstem and cardiac conduction system on serial sections but seldom do.