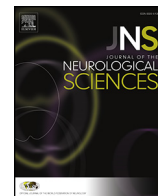




Contents lists available at ScienceDirect

## Journal of the Neurological Sciences

journal homepage: [www.elsevier.com/locate/jns](http://www.elsevier.com/locate/jns)

## Response to Letter to the Editor

**Reply to the Letter to Editor of Mage and Donner about the work “Developmental alterations of the auditory brainstem centers — pathogenetic implications in sudden infant death syndrome” (J Neurol Sci. 2015 doi: 10.1016/j.jns.2015.07.050)**

We realize that the Mage and Donner's observations do not refer specifically to our work on the alterations of the centers that control hearing in SIDS but rather on “the common belief (not only ours but also of other authors) that SIDS is a developmental defect of neurologic origin”. Basically they with this letter to the Editor highlight that there are two lines of thought about the significance of the neuropathological findings in SIDS, namely: 1) they are primary event and 2) they are secondary to hypoxia.

The first hypothesis is largely based on the observation that histopathological abnormalities, particularly of the brainstem, in SIDS cases have a prenatal origin and that the sudden death occurs in a vulnerable period of the infancy. The triple risk hypothesis of Filiano and Kinney [1] enshrines this concept predicting that fetal development of infants who succumb to SIDS is abnormal, leaving them unable to appropriately respond to stressors in a critical developmental phase of the homeostatic control. Accordingly, Randal et al. [2] maintain that exogenous, environmental factors can generate potentially lethal hypoxia and hypercapnia (i.e., homeostatic stressors), which in turn require intact brainstem defense systems to protect against death. Therefore SIDS is the result of an underlying brainstem congenital abnormality in neural networks that mediate protective responses to hypoxia.

Mage and Donner sustain the other hypothesis, in agreement with the Guntheroth and Spiers' theory [3], i.e. that the origin of SIDS is not prenatal and that brainstem alterations have not been shown to cause SIDS but rather, brainstem alterations are more likely an effect of hypoxia. In our opinion this could be appropriate as regards the observation of non-specific neuropathological changes spread throughout the brain, as gliosis or apoptosis. However, it is not readily apparent how this theory would explain the frequent findings of hypoplasia limited to specific brainstem nuclei involved in cardiorespiratory control, as the targeted effect of hypoxia in SIDS. The oxygen deficit can represent in these cases the trigger factor of homeostatic derangement leading to the fatal outcome.

In relation to the assertion that “SIDS is much more likely to be caused by an unobserved prodromal respiratory infection that fulminates suddenly, killing the infant quickly before gross lung parenchyma changes identifiable at autopsy present (8, page 156).....”, we firstly would point out that in the reference cited by Mage and Donner to support this sentence (Farber S. *Fulminating streptococcus infections in infancy as a cause of sudden death. NEJM* 1934, July 26, 154–159), the author illustrates an indisputable diagnosis at autopsy of pulmonary streptococcus infection in a seemingly perfectly well 3 month-old child's sudden death while sleeping on his back with his face uncovered. So, in this case, the diagnosis of “SIDS” is surely excluded.

We all are aware that SIDS is a diagnosis of exclusion, as stated in the current definition of SIDS, as “the sudden unexpected death of an infant <1 year of age, with onset of the fatal episode apparently occurring during sleep, that remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and the clinical history” [4].

In all cases of sudden and unexpected death in infancy (the so-called “SUDI”), the currently mandatory investigative protocol includes a post-mortem ancillary investigation [5]. Therefore, it's not possible that any respiratory infection able to cause a sudden death, can be undiagnosed.

We appreciate anyway the comments of Mage and Donner. All hypotheses and theories about the possible origin of SIDS are respectable and testify to the effort of the scientific world to highlight the pathogenetic mechanism of these very devastating events, hoping to be able to establish effective preventive measures addressed to significantly decrease the SIDS incidence.

*Since publication of the original article, the authors declare no further conflict of interest.*

## References

- [1] J.J. Filiano, H.C. Kinney, A perspective on neuropathologic findings in victims of the sudden infant death syndrome: the triple-risk model, *Biol. Neonate* 65 (1994) 194–197.
- [2] B.B. Randall, D.S. Paterson, E.A. Haas, K.G. Broadbelt, J.R. Duncan, O.J. Mena, et al., Potential asphyxia and brainstem abnormalities in sudden and unexpected death in infants, *Pediatrics* 132 (2013) e1616–e1625.
- [3] W.G. Guntheroth, P.S. Spiers, The triple risk hypotheses in sudden infant death syndrome, *Pediatrics* 110 (2002), e64.
- [4] H.F. Krous, J.B. Beckwith, R.W. Byard, T.O. Rognum, T. Bajanowski, T. Corey, et al., Sudden infant death syndrome and unclassified sudden infant deaths: a definitional and diagnostic approach, *Pediatrics* 114 (2004) 234–238.
- [5] The Royal College of Pathologists, The Royal College of Paediatrics and Child Health, Sudden unexpected deaths in infancy. A multi-agency protocol for care and investigation, The Royal College of Pathologists/The Royal College of Paediatrics and Child Health, London, 2004.

Anna Maria Lavezzi\*  
Giulia Ottaviani  
Luigi Maturri

*“Lino Rossi” Research Center for the study and prevention of unexpected perinatal death and SIDS Department of Biomedical, Surgical and Dental Sciences, University of Milan, Italy*

\*Corresponding author at: “Lino Rossi” Research Center for the study and prevention of unexpected perinatal death and SIDS Department of Biomedical, Surgical and Dental Sciences, University of Milan, Via della Commenda 19 20122 Milano, Italy. Tel.: +39 02 50320821; fax: +39 02 50320823.

E-mail address: [anna.lavezzi@unimi.it](mailto:anna.lavezzi@unimi.it)  
[http://users.unimi.it/centrolinorossi/en/index\\_en.html](http://users.unimi.it/centrolinorossi/en/index_en.html) (A.M. Lavezzi).

4 September 2015  
Available online xxxx