The brain beating and the heart breathing. Cardiorespiratory nuclei analysis and brainstem mapping in sudden infant death

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Objective: Sudden infant death syndrome (SIDS) is characterized by the death of an infant that cannot be explained, despite a systematic case examination, including death scene investigation, autopsy, and review of the clinical history. Sudden unexpected infant death (SUID) is a wide-ranging concept used to describe any sudden and unexpected death, whether explained or unexplained, including SIDS, which occurs during the first year of life. Differing hypotheses of the underlying mechanisms of SIDS have been proposed. The most reliable seems to be the "triple risk hypothesis". Based on this theory, SIDS might arise by the combination of three factors: a vulnerable infant, a vulnerable phase of development and a final insult occurring in this window of vulnerability. In the past, disjoined causes were recognized as main pathogenic conditions: primary cardiac alterations or primary respiratory anomalies or primary neurological predispositions. Recently, a unified neuropathological theory contributes to describe SIDS. Thanks to that, serotonergic neurons have a crucial homeostatic function in the cardiorespiratory brainstem centers. Materials: We investigated articles and reviews indexed in PubMed, queried databases of digital brain atlases to understand brainstem microcircuits involved in respiratory rhythm and in pattern generation for cardiorespiratory coupling. Contextually, we started to analyze brains and principally brainstems of SUID cases from 2014 until today. Methods: Cardiac, sympathetic, and respiratory motor activities can be viewed as a unified rhythm controlled by brainstem neural circuits for effective and efficient gas exchange. We improved the usual postnatal brain fixation, utilizing liquid solutions of glacial acetic acid in neutral-buffered formalin and ethanol. Results: By cardiorespiratory coupling theory and data from the literature, we obtained a scheme of cardiorespiratory brainstem nuclei network, and finally we mapped the principal cardiorespiratory nuclei of the human postnatal brainstem in 26 SUID cases. About 30% of our SUID cases presented anomalies of brainstem nuclei. Discussion: Many intrinsic and extrinsic factors increase SIDS susceptibility including prone sleeping position, inflammations, gender, prenatal nicotine exposure, and temperature. The final common pathway for SIDS involves a failure to arouse and autoresuscitate in response to environmental challenge. These risk factors can directly alter the function of cardiorespiratory nuclei and impair the ability of this network to coordinate cardiorespiratory coupling. Conclusions: Neuropathological analysis of the infant brainstem represents a good tool to infer on the final events of SUID and SIDS. An integrated study of postmortem functional imaging could help to understand the network of this beating-breathing-thinking unit.

Myo-miRNA and inflammatory microRNAs in muscle of sporadic and genetic ALS

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Objective: MicroRNAs are small non-coding RNAs that are associated with stress granules, mitochondria, and other subcellular organelles in muscle. Few studies have explored the role of microRNAs in muscle atrophy in amyotrophic lateral sclerosis (ALS). MiR-206, miR-133a, miR-133b, miR-1, and miR-27a are called "myo-miRNA" and are considered as markers of muscle regeneration, myogenesis, and fiber type differentiation. MiR-155, miR-146a, miR-221, miR-149* are involved in the inflammatory/angiogenic process. We previously observed that there is different serum microRNA profile in spinal versus bulbar ALS. We have investigated muscle biopsies in a series of ALS cases both sporadic and genetic and imply muscular regeneration at the level of neuromuscular junctions. Material and methods: We studied, in EI Escorial-proven ALS cases, muscle biopsies obtained for diagnostic purposes and requested to TMTB Biobank, myomicroRNAs (MiR-1;MiR-206; MiR-133a; MiR-133b; MiR-27a), and inflammatory microRNAs (MiR-155; MiR-146a; MiR-221; MiR-149*) by qRT-PCR. ALS cases were divided according to gender and age of onset. A series of cases had mutation of SOD and C9orf. The biopsies' morphologies were scored as + (slight atrophy), ++ (small group atrophy), +++ (group of atrophic fibers and connective tissue increase). Morphometric analysis of muscle fiber size was done to correlate muscle atrophy with molecular parameters. Results and discussion: All microRNAs studied were strongly upregulated in muscle biopsies of ALS patients versus controls with the exception of miR-149*. Significant overexpression of miRNAs was present in genetic versus sporadic ALS and in male versus female gender. The morphologic score utilized confirmed a muscle fiber atrophy in ALS patients compared to controls. Genetic ALS (SOD, C9orf) were atrophic with high fiber variability. Conclusions: These results provide evidence of the molecular role of microRNAs in correlation to muscle atrophy. In addition, we observed an increased expression of microRNAs in genetic ALS and dysregulation of inflammatory microRNAs. The upregulation of myomiRNAs we found correlates with the degree of atrophy and possible regeneration process of neuromuscular junction.

TSC-associated central nervous system lesion: different lesions with a common pathogenesis

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Objective: Tuberous sclerosis complex (TSC) is a dominantly inherited disease caused by mutations in either TSC1 or TSC2 genes leading to hyperactivation of mTORC complex with development of hamartomas in different organs and se-