

# Sudden unexpected postnatal collapse at 20 hours from birth during skin-to-skin care related to brainstem developmental alterations – a case report

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*Folia Neuropathol* 2017; 55 (3): 235-241

DOI: <https://doi.org/10.5114/fn.2017.70489>

## Abstract

*This report describes a case of sudden collapse of a 20-hour-old newborn, while he was placed close to their mother according to skin-to-skin care, attributed to developmental alterations of brainstem nuclei involved in regulation of the vital functions. The infant, after a normal pregnancy, appeared well developed at birth, with no evidence of malformations or trauma, but showing severe asphyxia. The routine autopsy did not reveal a possible cause of death. Only the in-depth anatomopathological examination of the autonomic nervous system, according to the protocol developed by the “Lino Rossi” Research Center of Milan University, provided an explanation of the pathogenetic mechanism of this early death. The sudden death, a few hours after birth, was the unavoidable outcome of a complex of abnormalities of brainstem nuclei, particularly of the Kölliker-Fuse nucleus, an essential structure for eupneic breathing at birth, exacerbated by the prone position implied by the skin-to-skin contact.*

**Key words:** early SIDS, brainstem, neuropathology, collapse, skin-to-skin contact, Kölliker-Fuse nucleus, retrotrapezoid nucleus, raphe obscurus nucleus.

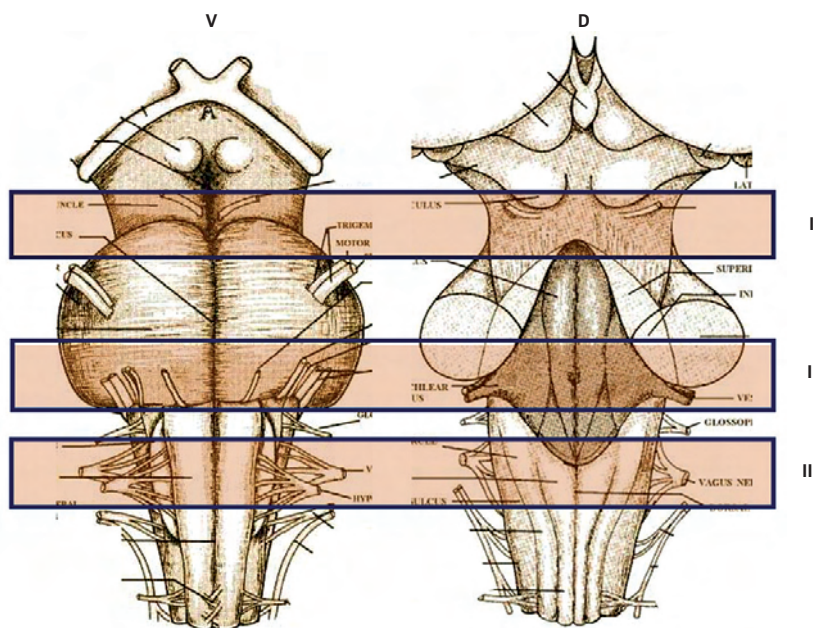
## Introduction

Sudden intrauterine unexplained death syndrome (SIUDS) and sudden infant death syndrome (SIDS) are very frequent events that represent, despite modern advances in maternal-infant care, major unresolved social and health problems of current medicine

[10]. To identify possible pathogenetic mechanisms of these deaths, the Law “Regulations for Diagnostic Post Mortem Investigation in Victims of Sudden Infant Death Syndrome (SIDS) and Unexpected Fetal Death” was introduced in 2006 in Italy [1]. This law stipulates that all infants who die suddenly within one year of life without any apparent cause, and

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**Fig. 1.** Schematic representation of the brainstem sampling (V: ventral surface; D: dorsal surface): I – pontomesencephalic specimen, including the upper third of the pons and the adjacent portion of the mesencephalon, II – caudal pontine specimen, III – medulla oblongata specimen, including the obex.

fetuses that die after the 25<sup>th</sup> week of gestation without any apparent cause, must be rapidly submitted to an in-depth diagnostic post mortem investigation, following specific guidelines drawn up by the “Lino Rossi” Research Center of Milan University that include, in particular, careful examination of the autonomic nervous system.

The Law has been intensively applied above all in Northeast Italy, allowing one to investigate numerous cases of sudden fetal and infant death and to identify, consistently, the presence of developmental alterations of neuronal centers prevalently located in the brainstem [14].

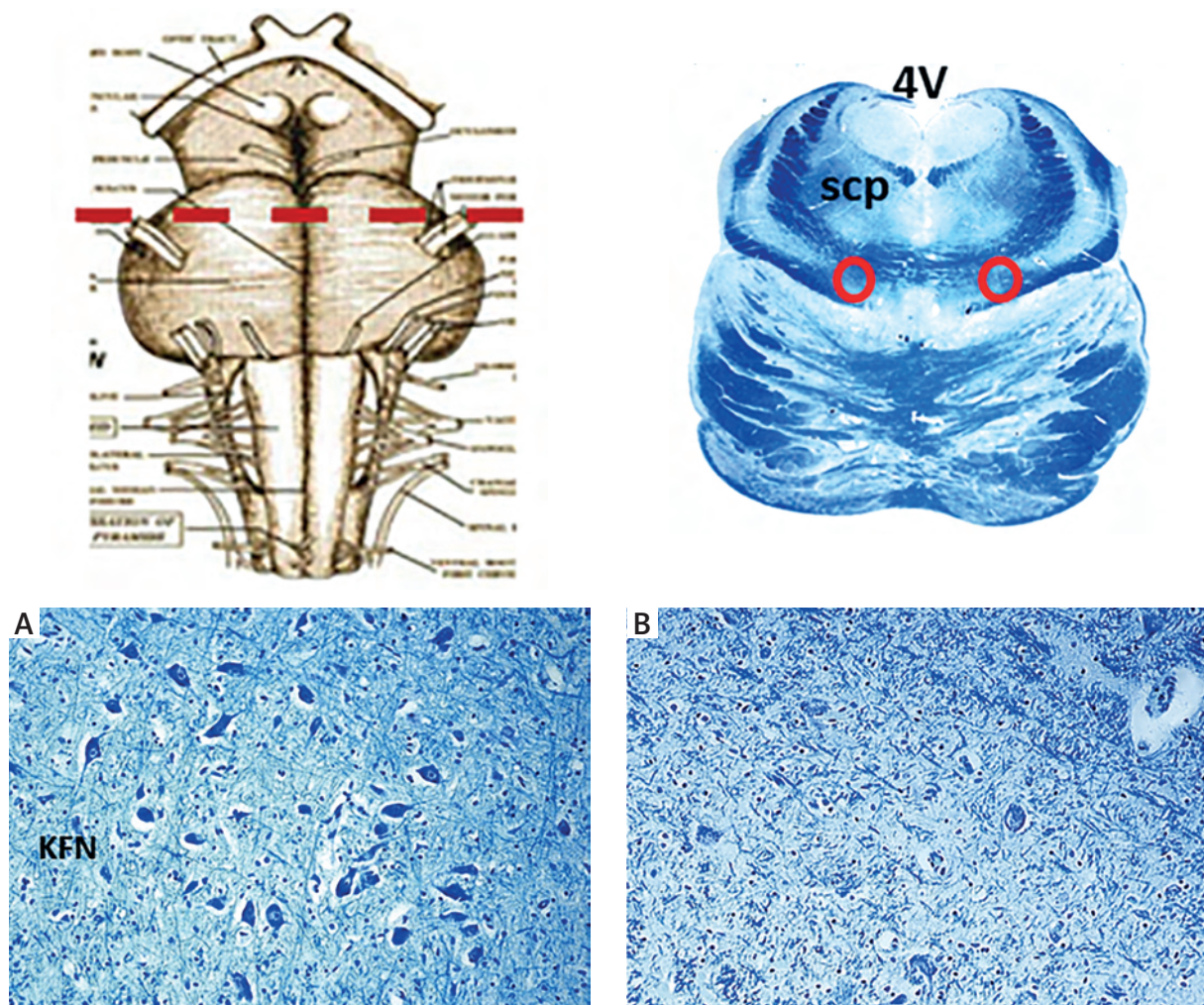
Below, we report one of these cases which deserves to be highlighted. This is a sudden death occurring at 20 hours from birth during skin-to-skin care, which was unexplained after a routine autopsy. However, the anatomopathological examination of the autonomic nervous system revealed the presence of hypodevelopment of several brainstem nuclei, above all of the pontine Kölliker-Fuse nucleus, an essential vital nucleus at birth.

### Case report

After a 41-week normal pregnancy and an uncomplicated labor and delivery, a very serious, unexpect-

ed and unexplained asphyxia was detected in a newborn at birth (Apgar score at 5 min: 0). Although heart activity appeared just minutes from birth, following repeated administration of adrenaline, death occurred 20 hours following delivery, while the baby was placed on his mother’s chest. The infant appeared well developed with no evidence of malformations or trauma. His parents stated that they had had no illness of any nature. There was no significant family history relevant to the case. The mother was also asked about drug or alcohol abuse and smoking before and during pregnancy, but she denied these risk factors.

Birth infant weight was 3030 g, length 49 cm and head circumference 32.8 cm. Multiple samples of all organs were collected at routine autopsy, then fixed in 10% formalin buffer, processed, and embedded in paraffin. Five-micrometer (5 µm) sections were then obtained from every sample and stained with hematoxylin/eosin. All the organs appeared unremarkable at gross and microscopic examination. What then could be the cause of the unexpected asphyxia and of the consequent death occurred at birth? The in-depth anatomopathological examination of the brainstem, according to the following protocol, provided a possible explanation.



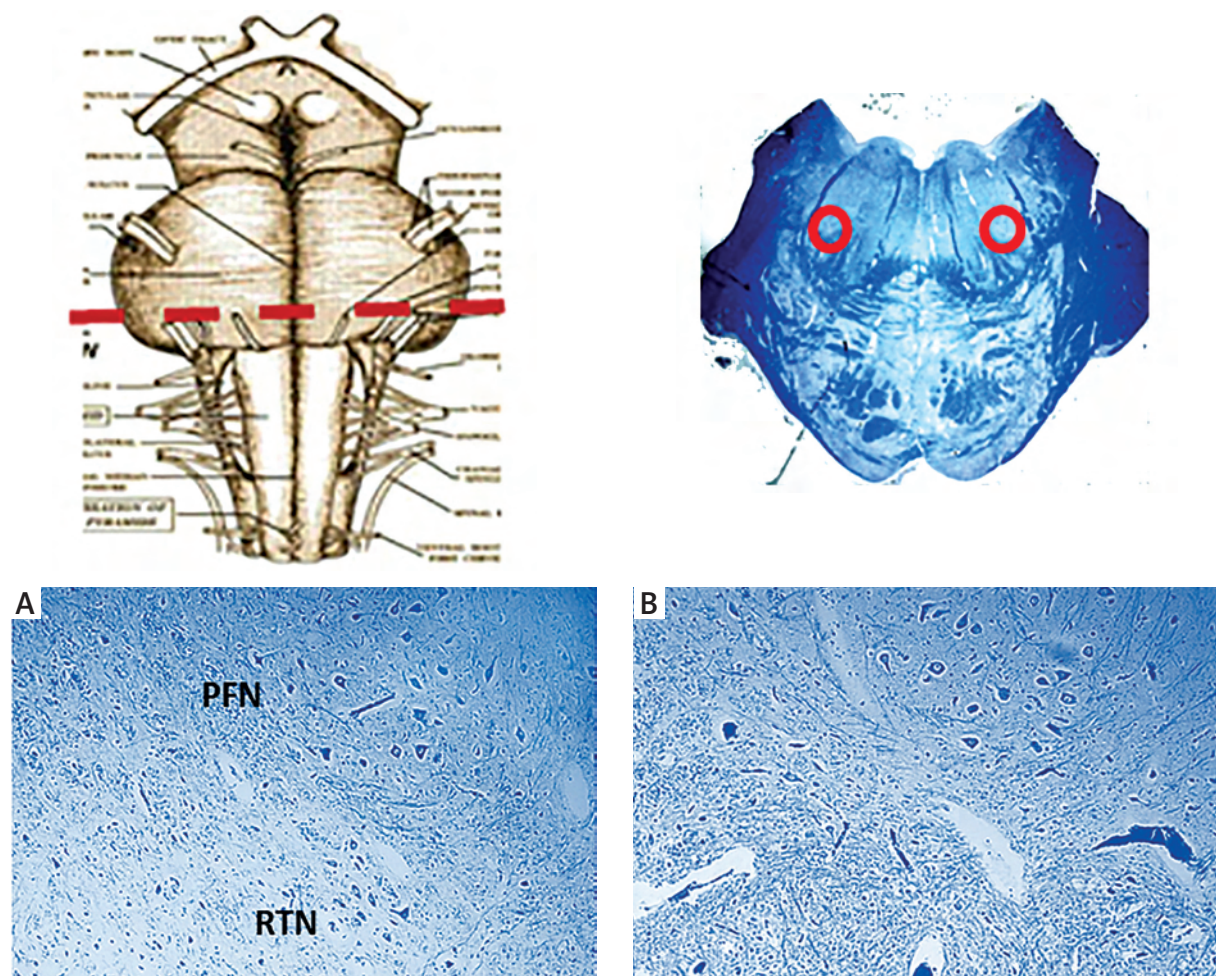
**Fig. 2.** Image series related to the Kölliker-Fuse nucleus (KFN). Top left: ventral brainstem image with indication of the optimal level for examination of the KFN; right: histological section at the above-mentioned level with bilateral localization of the KFN (encircled area). **A)** Normal cytoarchitecture of the KFN showing large neurons with a distinct nucleus and evident nucleolus. **B)** Hypoplasia of the KFN with very few neurons. 4V – fourth ventricle; scp – superior cerebellar peduncle. Klüver-Barrera stain, magnification **(A)** and **(B)** 100 $\times$ , at top 0.5 $\times$ .

### Neuropathological examination of the brainstem

Briefly, the applied methodology, in accordance with the aforementioned guidelines provided by Italian law, states that, after fixation in 10% phosphate-buffered formalin, the brainstem, where the main structures controlling the vital functions are located, must be processed and embedded in paraffin. Then three specimens are taken (Fig. 1): the first specimen (I) includes the upper third of the pons and the adjacent caudal portion of the midbrain; the second speci-

men (II) is taken from the caudal portion of the pons; and the third specimen (III) is from the medulla oblongata around the obex. Transverse serial sections from all the samples are made at intervals of 60  $\mu$ m. For each level, twelve 4  $\mu$ m sections are obtained, two of which are routinely stained for histological examination using alternately hematoxylin-eosin and Klüver-Barrera methods. Additional sections are saved and stained as deemed necessary for further investigations. The main nuclei are then analyzed: the parafacial nucleus, the retrotrapezoid nucleus, the locus coeruleus, the Kölliker-Fuse nucleus and the median,





**Fig. 3.** Image series related to the retrotrapezoid nucleus (RTN). Top left: ventral brainstem image with indication of the optimal level for examination of the RTN; right: histological section at the above-mentioned level with bilateral localization of the RTN (encircled area). **A)** Normal cytoarchitecture of the RTN showing a group of small neurons adjacent to the parafacial nucleus (PFN). **B)** Hypoplasia of the RTN with very few neurons. Klüver-Barrera stain, magnification **(A)** and **(B)** 100×, at top 0.5×.

magnus, dorsal, caudal and linear raphe nuclei in the pons; the hypoglossus, the dorsal motor vagal, the tractus solitarius, the ambiguus, the pre-Bötzinger, the inferior olivary, the arcuate and the obscurus and pallidus raphe nuclei in the medulla oblongata.

Consent: Written informed consent was obtained from the parents of infant for the autoptic examination and related research. Study approval was granted by the institutional review board of Milan University (“Lino Rossi” Research Center).

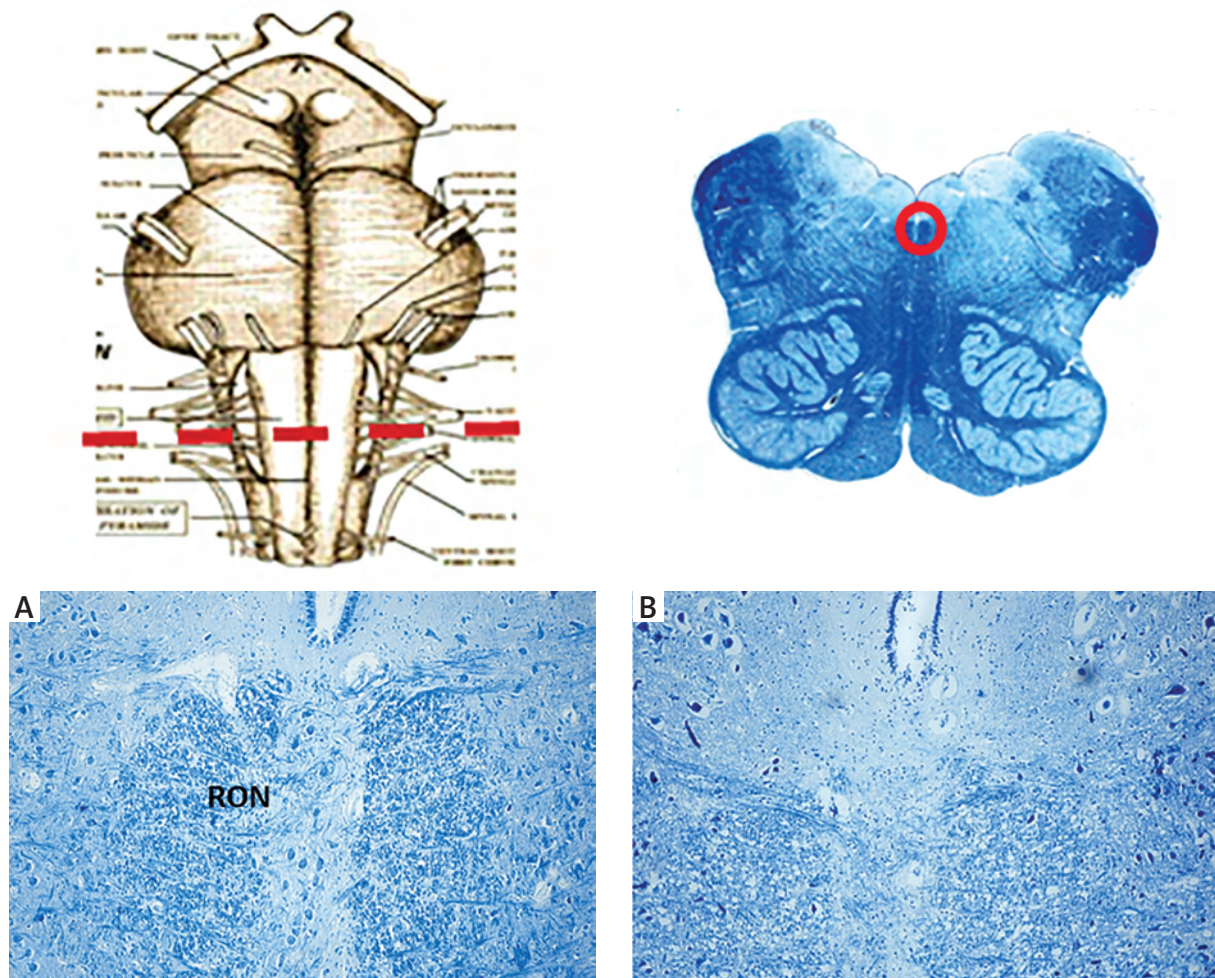
### Results of neuropathological examination

The histological analysis of the brainstem showed a normal cytoarchitecture in relation to age, i.e. com-

pared with the normal structure of age-matched controls, of almost all the above-mentioned nuclei. However, severe hypoplasia of the Kölliker-Fuse nucleus in the rostral pons (Fig. 2B) and hypodevelopment of the retrotrapezoid nucleus in the caudal pons (Fig. 3B) and of the obscurus raphe nucleus in the medulla oblongata (Fig. 4B) were diagnosed.

### Discussion

The case presented here is of particular interest as the death occurred inexplicably on the first day of life, while the baby was face-down during skin-to-skin care. It is generally understood that SIDS affects infants



**Fig. 4.** Image series related to the raphe obscurus nucleus (RON). Top left: ventral brainstem image with indication of the optimal level for examination of the RON; right: histological section at the above-mentioned level with localization of the RON (encircled area). **A)** Normal cytoarchitecture of the RON showing a group of neurons distributed along the middle line. **B)** Hypoplasia of the RON with very few neurons. Klüver-Barrera stain, magnification **(A)** and **(B)** 100 $\times$ , at top 0.5 $\times$ .

1 month to 1 year old and that the sudden unexpected death of an apparently healthy term infant within the first day of life is a rare event. However, a recent report by Save the Children indicates that over one million newborns around the world die each year on their first day of life [2]. The initial 24 hours are indicated as the most critical and dangerous for life, and the present case confirms this assertion.

While the routine autopsy revealed no cause of death, the results obtained from the deep examination of the autonomic nervous system highlighted subtle developmental abnormalities of the brainstem nuclei controlling the vital functions. The most important alteration, sufficient to explain the patho-

genetic mechanism of death, was the severe hypoplasia of the Kölliker-Fuse nucleus observed in the rostral pons.

The Kölliker-Fuse nucleus consists of a small group of neurons that have an important function during intrauterine life, inhibiting the response of central and peripheral chemoreceptors (which are already fully formed and potentially functional) and therefore any respiratory reflex. At birth, the Kölliker-Fuse nucleus abruptly reduces its inhibitory effects and becomes active as the main respiratory center, both stimulating the parafacial and pre-Bötzinger nuclei, assigned to promote the first inspirations, and coordinating the pulmonary motor responses to hematic



oscillations of  $pO_2$ ,  $pCO_2$  and pH [5-8]. This activity is also sustained by the chemoreceptor nuclei, to which the retrotrapezoid nucleus and the raphe obscurus nucleus belong [3,9].

Then, the severe asphyxia at birth can be explained by the hypoplasia of the Kölliker-Fuse nucleus, able to prevent the start of the eupneic breathing usually initiated by the parafacial and pre-Bötzinger nuclei under its control, despite their normal development. The hypoplasia of the retrotrapezoid and the raphe obscurus nuclei contributed to the lack of ventilatory response to altered levels of the hematic parameters, so further contributing to death. The face pressed against the mother's chest due to the skin-to-skin position, reducing the amount of oxygen supplied to the brain, has accelerated the fatal outcome.

In our previous studies, we have reported the implication of the Kölliker-Fuse nucleus in the pathogenesis of SIDS and that its hypoplasia, like other brainstem alterations, is significantly associated with maternal smoking in pregnancy [5,8]. In this case however the mother admitted no history of cigarette smoking. Furthermore, it should be considered that retrospective assessment of maternal smoking, mainly if performed after the fatal event, is sometimes unavoidable [18]. Not rarely, smoking mothers are reluctant to honestly report their tobacco use, possibly because of feelings of guilt. In addition to nicotine, other risk factors for delayed development of brain nuclei should be considered. Recently, original investigations have demonstrated the adverse effects of persistent pollutants such as pesticides and household insecticides (belonging to the category of endocrine disrupting compounds [EDCs]) on brain development [12,13,15,16]. Traces of highly toxic chemicals, such as organochlorine and organophosphate pesticides ( $\alpha$  and  $\gamma$ -chlordane, chlorfenvinfos, chlorpyrifos, p,p-DDT, p,p-DDE, endrin,  $\alpha$ - and  $\beta$ -endosulfans), have been directly detected in cerebral cortex samples of several SIUDS/SIDS cases, frequently from agricultural areas where pesticides are used. These interactions can directly impair autonomic nervous system development, resulting in hypoplasia of the main brainstem centers controlling the vital functions, and consequently leading to sudden death.

This case report indicates that also the skin-to-skin contact can be considered as a risk factor for sudden neonatal deaths and that it is imperative to provide to the medical and nursing personnel, as well as mothers,

accurate information regarding this care and the related risk of collapse. Finally, we underline the need for an in-depth examination of the central nervous system in victims of sudden perinatal death. The neuropathological protocol applied by our research team [17], and briefly described here, should become a specialized component of the fetal and infant autopsy, above all when a clear cause of death is not found. The universal application of this procedure is the best way to collect a rich body of information about all possible neurological alterations in the newborn brain, in order to reduce their incidence and mitigate the related social impact.

## Disclosure

Authors report no conflict of interest.

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