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Hippocampal asymmetry and sudden unexpected death in infancy: a case report

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Abstract

The differential diagnosis of known entities associated with sudden unexpected death in infancy is ever expanding. Here we report the case of a 10-month-old infant boy whose clinical presentation mimicked that of the sudden infant death syndrome (SIDS). This presentation included the typical features of SIDS: sleep-related death; prone position upon discovery; and minor illness within 2 days of death. Nevertheless, neuropathologic examination revealed striking hippocampal asymmetry and microdysgenesis similar to that reported previously by us in toddlers with sleep-related sudden death. Hippocampal maldevelopment in the setting of sudden death in infants and toddlers is analogous to sudden unexpected death in epilepsy associated with temporal lobe pathology, and suggests a possible role for seizures in the terminal events leading to sudden death. This report serves to alert pediatric and forensic pathologists to hippocampal asymmetry and microdysgenesis in the differential diagnosis of sudden infant death mimicking SIDS.

Keywords

Apnea; Febrile seizures; Microdysgenesis; Sudden infant death syndrome (SIDS); Sudden unexpected death in epilepsy (SUDEP); Temporal lobe

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Introduction

The hippocampus is a major brain region critical to respiratory and autonomic control [1, 2]. We recently reported the association of sudden unexplained death in childhood (SUDC) with asymmetry and microdysgenesis of the hippocampus and other temporal lobe abnormalities in toddlers (1–5 years old) with or without a personal or family history of febrile seizures [3, 4]. This disorder in toddlers suggests a possible variant of sudden and unexpected death in epilepsy (SUDEP) in the preschool age group [3, 4]. SUDEP is defined as the sudden and unexplained death in patients with a known history of epilepsy that is not related to trauma, accidents, or status epilepticus [5]. It has been reported in older individuals with hippocampal abnormalities [6–8]. The question arises whether hippocampal asymmetry similar to that reported in toddlers can be associated with sudden death in *infants*. Below, we report the case of a 10-month-old boy whose death was originally classified as the sudden infant death syndrome (SIDS)—the sudden death of an infant younger than 12 months of age that is related to a sleep period and unexplained by a complete autopsy and death scene investigation [9]—but in whom neuropathologic examination revealed asymmetry of the hippocampus and microdysgenesis similar to that reported in toddlers who were initially also classified as SUDC [3, 4].

Case report

The infant was the product of a 40–41 week normal pregnancy except for mild maternal hypertension in the last trimester. The labor and delivery were uncomplicated; the Apgar score at 5 min was 9. Birth weight was 2,985 g (10 %ile), birth length 50.6 cm (25 %ile), and head circumference 32 cm (10 %ile). The infant was discharged from the routine nursery at 2 days of age without complications. He was routinely placed in the side position to sleep in a crib alone in a separate room. Developmental milestones were appropriate. Home videos at 6, 8, 9, and 10 months that were made available to us by the family revealed an alert, interactive infant without apparent neurological abnormalities. There was no history of apparent life-threatening events, or febrile or afebrile seizures. Immunizations were up to date. Within 48 h of death at 10 months, the infant developed a “cold” with nasal congestion, “unsettled sleep,” mild diarrhea, but no fever. On the night of death, he was placed on the side to sleep in the crib in lightweight sleeping clothes at approximately 11:30 pm. The mother last heard the infant breathing via the baby monitor at approximately 6:30 am. He was then found pale, not breathing, and unresponsive by his mother at 8:15 am. He was in the prone position with his head turned to the right side and his airway unobstructed. Resuscitative efforts were unsuccessful. There was no family history of seizures, other neurological disorders, or cardiac disorders.

The autopsy revealed a well-developed infant with no evidence of trauma. There was a resolving focal bronchiolitis in the lung and chronic inflammatory cell infiltrates in the larynx and epiglottis. There were no intrathoracic petechiae, or cardiac abnormalities. The ancillary studies were non-contributory. The scene investigation excluded accidental processes or environmental hazards. The coroner classified the death as SIDS.

Neuropathologic analysis

External examination of the brain

The unfixed brain weighed 1,032 g (normal: 809 g [range: 750–852 g]). There was no subdural hematoma. The leptomeninges were transparent with no hemorrhage or pus. There was mild flattening of the gyri and narrowing of the sulci, suggestive of cerebral edema in conjunction with the heavy brain weight; transtentorial herniation was not present. The

vertebral arteries were asymmetric with the left (0.3 cm) larger than the right (0.2 cm); the posterior communicating arteries were also asymmetric with the right (0.2 cm) greater than the left (0.1 cm). The basilar artery and circle of Willis were otherwise unremarkable. The temporal lobe gyri and insulae were well formed externally; the opercula were closed.

Upon coronal sectioning in approximately 0.5 cm slices, asymmetry of the hippocampi was appreciated (Fig. 1). At the anterior level (level of the red nucleus of the midbrain), the left pes appeared globular and foreshortened in the mediolateral plane (Fig. 1a). At the level of the lateral geniculate nucleus, the left hippocampus was slightly flattened and elongated in the mediolateral plane, and the temporal horn of the lateral ventricle appeared dilated (Fig. 1b). At the posterior level (level of the pineal body and tail of the caudate), the left hippocampus was markedly flattened and appeared smaller than the right hippocampus, and the dilatation of the temporal ventricle was striking (Fig. 1c). The regional ventricular dilatation of the left temporal pole suggested compensation for the small hippocampus. The left and right parahippocampal gyri appeared intact bilaterally. Upon coronal sectioning, the lateral temporal lobes were well formed, with distinct superior, middle, and inferior temporal gyri (Fig. 1). The cortical ribbon was of appropriate thickness without infarcts or hemorrhage. The white matter was well myelinated grossly with no periventricular cysts or necrotic foci. The thalamus, basal ganglia, amygdala, hypothalamus, and cerebellum were free of macroscopic lesions. The right and left hippocampi were submitted in toto in four blocks on each side for microscopic examination.

Microscopic examination

Abnormal findings were limited to the hippocampi and temporal lobes; of note, the brainstem (including a single section of the medulla oblongata) was unremarkable. Asymmetry of the hippocampus was appreciated due to anomalies in the shape and size of the hippocampus proper and degree of convolution of the dentate gyrus (Fig. 2). At the level of the lateral geniculate nucleus, the degree of rotation of the left and right hippocampi was not symmetric, with the left slightly more flattened and displaced laterally than the right (Fig. 2a). The left dentate gyrus appeared more convoluted than the right (Figs. 2a, 3). At the posterior level (level of the tail of the caudate), the left hippocampus was flattened in the mediolateral plane and did not demonstrate the degree of rotation of the right side (Fig. 2b). Microdysgenesis features were noted on one or both sides and included: (1) mild hyperconvolution of the left dentate gyrus (Figs. 2a, 3); (2) hamartia (clusters of tightly packed immature cells) in the wall of the right temporal horn (Fig. 3); (3) a granular heterotopia (ectopic collection of granular neurons) in the hippocampus proper which did not fuse with the dentate gyrus at any level upon step sectioning (Fig. 3); and (4) microscopically fused gyri (probable middle and inferior gyri) were in right lateral temporal lobe (Fig. 3). Focal clusters of granule neurons in the molecular layer of the dentate gyrus were also noted bilaterally (Fig. 3). There was no loss of neurons, astrogliosis, or microglial activation in the dentate gyrus or Ammon's horn.

Hippocampal survey

In order to assess the incidence of microdysgenetic features in the human postnatal hippocampus, we retrieved available microscopic sections of the hippocampus from all recent autopsied cases of children at our hospital, irrespective of the cause of death. In each case, 1–2 sections of the hippocampus, stained with hematoxylin-and-eosin or hematoxylin-and-eosin/Luxol-fast-blue, were examined at the level of the lateral geniculate nucleus. We examined the hippocampus in 25 cases from term birth to 19 years, with a median of 5 years. There were 5 cases between 2.5 and 16 postnatal months (median, 5 months), the age range that bracketed the age of the present case. Three of the cases had a history of seizures complicating the agonal course; none of the cases had a history of epilepsy. Causes of death

were the following: neoplasia, *n* = 10; primary lung disorder, *n* = 5; infection, *n* = 3; congenital heart disease, *n* = 3; primary immunological disorder, *n* = 1; muscular dystrophy, *n* = 1; Down's syndrome (with normal hippocampus) *n* = 1; and perinatal asphyxia, *n* = 1. The incidence of the following microdysgenetic features was: granular heterotopia, 8 % (2/25); focal duplication of the dentate gyrus, 4 % (1/25); periventricular hamartia, 0 % (0/25); hyperconvolution of the dentate gyrus, 0 % (0/25); and microscopic fusion of temporal gyri, 0 % (0/25).

Discussion

We report here hippocampal asymmetry and microdysgenesis discovered at autopsy in an infant with sudden and sleep-related death mimicking the clinical presentation of SIDS. The present case implicates a role for hippocampal pathology in sleep-related sudden death in infants similar to that postulated by us in toddlers with hippocampal anomalies and sudden death related to a sleep period [3, 4]. In the series reported by us of toddlers with SUDC, 47 % (7/15) of SUDC cases without a personal and/or family history of febrile seizures had hippocampal anomalies [4], as found in our case. That is, hippocampal maldevelopment was not always associated with febrile seizures in early life, and thus such seizures are apparently not essential in the chain of events leading to sudden death. Sudden death in these cases may result from a cardiac arrhythmia or respiratory arrest that originates from an epileptogenic discharge in an abnormal temporal lobe, by analogy to a proposed mechanism of SUDEP associated with temporal lobe pathology [6–8, 10]. The present case demonstrates that temporal lobe pathology can be found before, as well as after, the 1-year mark that arbitrarily divides SIDS from SUDC, and as such, likely represents a congenital abnormality that can present clinically at different times prior to school age.

The findings of granular heterotopia, clusters of granule cells in the molecular layer of the dentate gyrus, and periventricular hamartia in the present case are microdysgenic features indicative of abnormal development in neuronal migration [8, 10–12]. Microdysgenetic features in isolation can be found in non-epileptic brains, and their significance in epileptic brains has been controversial, with hamartia, but for one example, linked [8, 10] and not linked [11] to epilepsy; nevertheless, they have been interpreted as markers of subtle underlying brain maldevelopment in patients with epilepsy [7, 8, 12]. In an archival survey of 26 hippocampi in recently autopsied cases, we found that the incidence of granule cell clusters or duplication of the dentate gyrus was less than 5 % and granular heterotopia, less than 10 %, with no detection of granular heterotopia, hamartia, or fused temporal lobe gyri —indicative that these findings are not common in the general pediatric autopsy population, a conclusion supported by previously published reports [12].

In our case, the main clinical features mimic those typical in SIDS infants, notably history of minor illness within days of the death, prone position when found, and death related to a sleep period [9, 13]. These similarities raise the question of whether there may be hippocampal anomalies, however subtle, in a larger population of SIDS infants that have not been previously appreciated. Yet, developmental anomalies in the temporal lobes have not been reported in SIDS [13]. The obvious feature that distinguishes SUDEP from SIDS is that SIDS infants do not have a history of epilepsy, whereas SUDEP patients had epilepsy by definition. In addition, febrile seizures have not been reported in SIDS infants [14]. Nevertheless, seizures are a consideration in the pathogenesis of SIDS, given that single or recurrent episodes of apnea, reported in certain infants who subsequently die of SIDS [15], may be the sole manifestation of seizures in newborns and infants with temporal lobe pathology [16]. Recent parallels have also been made between SIDS and SUDEP, including the occurrence in both entities of defects in the central serotoninergic network [5, 13]; moreover, it has been suggested that SUDEP and SIDS share common mechanisms that

involve serotonin [5]. We speculate that our patient represents a case analogous to SUDEP presenting as SIDS in which the initial seizure may have been related to the observed temporal lobe pathology and was fatal. Subcellular defects in the hippocampus may potentially characterize a larger subset of SIDS cases without gross temporal lobe pathology, calling for the need for future neurochemical/molecular analysis in SIDS cases.

In conclusion, this report alerts forensic pathologists to maldevelopment of the hippocampus in the differential diagnosis of sudden and unexpected death in infants that mimics the clinical presentation of SIDS. Comprehensive examination of the temporal lobes bilaterally should be performed in any case of sudden unexpected death without apparent cause in infancy and beyond.

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Key points

1. We report the association of sudden and unexpected death in an infant with asymmetry and microdysgenesis of the hippocampus.
2. Temporal lobe maldevelopment should be considered in the differential diagnosis of sudden and unexpected death in infants that mimics the clinical presentation of the sudden infant death syndrome.
3. Hippocampal maldevelopment in the setting of sudden death in infants is analogous to that in toddlers, as well as in sudden unexpected death in epilepsy associated with temporal lobe pathology, and suggests a possible role for seizures in the terminal events leading to sudden death.
4. Comprehensive examination of the temporal lobes bilaterally should be performed in any case of sudden unexpected death without cause.

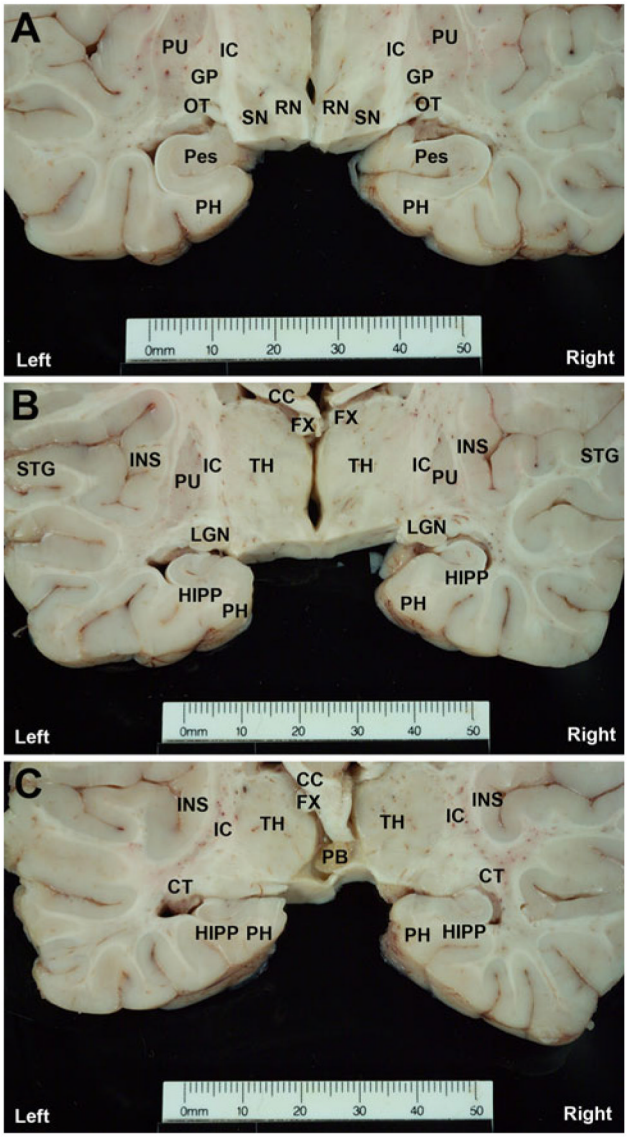

Fig. 1.

There is macroscopic asymmetry of the hippocampus in the reported 10-month-old infant boy with sudden and unexpected death. The macroscopic abnormalities are restricted to the hippocampus. **a** At the anterior level (level of the substantia nigra and red nucleus), the *left pes* appeared globular and shortened in the mediolateral plane. **b** At the mid level (level of the lateral geniculate nucleus), the *left hippocampus* was slightly flattened and elongated in the mediolateral plane, and the temporal horn of the lateral ventricle appeared slightly dilated. **c** At the posterior level (level of the pineal body and tail of the caudate), the *left hippocampus* was markedly flattened and appeared smaller than the *right side*, and the dilatation of the temporal ventricle was increased. The parahippocampal gyri, and superior, middle, and inferior temporal gyri appeared intact. *Abbreviations: CC* corpus callosum, *CT* tail of the caudate, *FX* fornix, *HIPP* hippocampus, *GP* globus pallidus, *IC* internal capsule, *IN* insula, *LGN* lateral geniculate nucleus, *OT* optic tract, *PB* pineal body, *PE* pes of hippocampus, *PH* parahippocampal gyrus, *PU* putamen, *RN* red nucleus of midbrain, *SN* substantia nigra of midbrain, *TH* thalamus

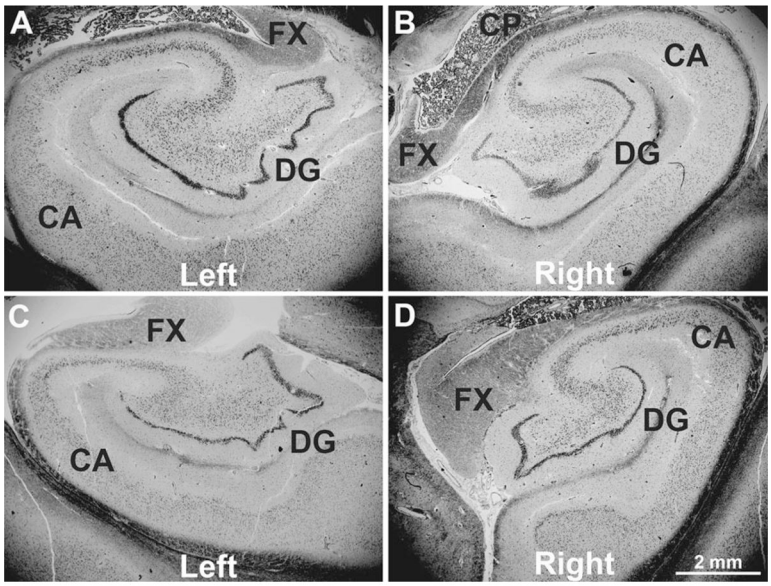

Fig. 2.

Asymmetry of the hippocampus is appreciated due to anomalies in the shape and size of the hippocampus proper and degree of convolution of the dentate gyrus. **a** Level of the lateral geniculate nucleus: the degree of rotation of the left and right hippocampi is not symmetric, with the *left* slightly more flattened and displaced laterally than the right. This level corresponds to that of Fig. 1b. **b** Level of the tail of the caudate: the *left hippocampus* is flattened in the mediolateral plane. This level corresponds to that of Fig. 1c. *Abbreviations: CA* cornu ammonis, *CP* choroid plexus, *CT* tail of the caudate nucleus, *DG* dentate gyrus, *FI* fornix. Scale bar = 2 mm

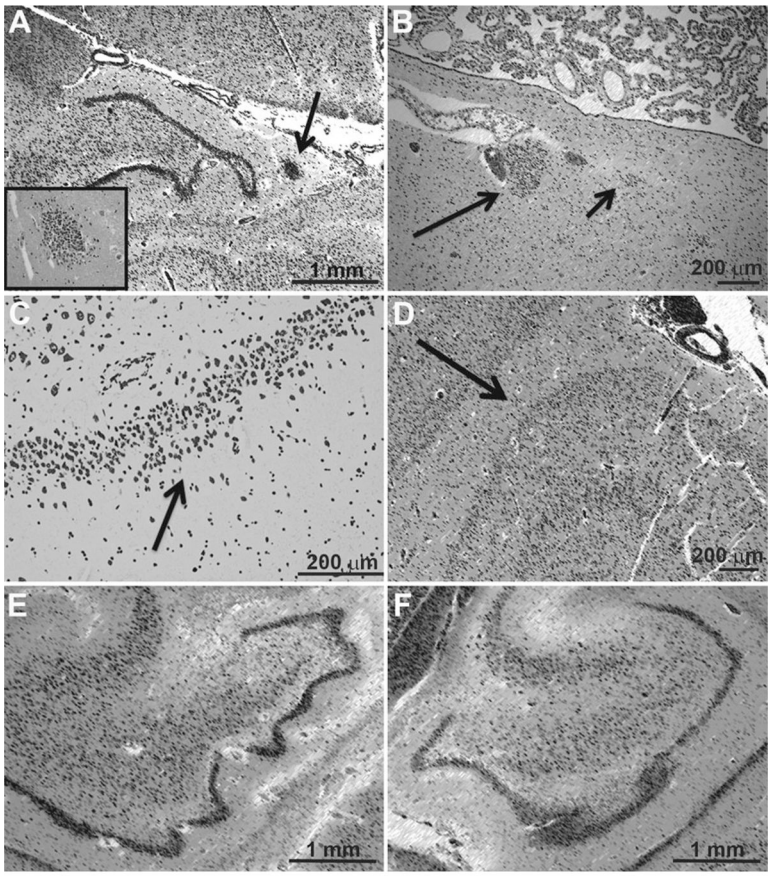

Fig. 3.

Microdysgenesis of the temporal lobe in the reported case with macroscopic asymmetry of the hippocampus. **a** Granular heterotopia (*arrow*) is present and distinct from the *left dentate gyrus*, as confirmed upon step sections (×10 magnification). *Insert*: A cluster of granular neurons comprises the heterotopia (×40 magnification). **b** Several hamartia (*arrows*) are present in the subventricular zone of the right temporal horn of the lateral ventricle (×10 magnification). **c** There is focal duplication of the dentate gyrus, as shown on the *left side* (*arrow*) (×20 magnification). **d** There is fusion of two temporal lobe gyri (*arrow*) on the right side (×10 magnification). **e** There is mild hyperconvolution of the dentate gyrus (DG), as appreciated in the left hippocampus proper (*arrow*) compared to the *right*. All microscopic sections are stained with hematoxylin-and-eosin or cresyl violet. Variable *scale bars*