Diagnosis | 'Space cadet' syndrome of female FVB/n mice

At a 1999 NIH Symposium on transgenic mice, Deborah E. Devor-Hennemann reported a syndrome of sudden death and variable CNS lesions in both transgenic and wildtype populations of FVB mice and named it 'space cadet' syndrome (SCS)[2]. The behavioral manifestations of this syndrome, including withdrawal from social interaction, led to the unique and memorable name. A previous report has shown that while both sexes are affected, females are more predisposed to SCS[3]. Some investigators have defined this condition as a neuroendocrinological disorder that may be the result of a mutation first reported in the FVB/NCr subline and lines derived from NCr stock[2]. Others hypothesize that this syndrome represents a potentially longstanding condition of FVB mice that had not been previously reported[2]. SCS is thought to be the result of neuronal necrosis in the brain from seizure activity and its associated hypoxemia, leading to the behavioral changes in survivors[4]. Histologically, these degenerative brain lesions are characterized by neuronal degeneration and necrosis (**Fig. 1a**), predominantly seen in the thalamus, but also appearing in the cerebral cortex and hippocampus. Concurrent astrocyte hypertrophy (or astrocytosis) in the areas of neuronal necrosis, as evidenced by an increase in glial fibrillary acidic protein (GFAP) staining (**Fig. 2a**), results eventually in gliosis (the production of a dense fibrous network of neuroglia).

SCS has been linked to reduced fertility, aggression toward cagemates, and excessive postpartum infanticide. This condition should be considered as a differential diagnosis in the likely causes of death in otherwise clinically healthy female FVB/n mice[3]. SCS should also be a differential diagnosis for either abrupt behavioral changes among littermates or an unexpected change in breeding production within a FVB colony of mice.

Other clinical signs reported in SCS include seizures (which may be fatal) and hyper-reactivity to stimuli. Seizures are the most probable cause of death in the mice in this report, as this is consistent with the lack of gross lesions in most of the animals. The presence of saliva on the ventrum of the neck in the animals described here also supports the possibility of an episode of convulsing or overactive chewing just prior to death. There has been no definite link to external stimuli resulting in increased seizure activity, though the association of the syndrome in these mice with movement to different rooms within the facility is an intriguing observation that might suggest an etiology for increase in audiogenic seizure activity.

Gross pathological changes associated with SCS that were not seen in the mice reported here include distention of the urinary and gall bladders, adrenal hypertrophy, and brain hypertrophy, possibly secondary to widespread gliosis[2]. Histopathological findings noted in SCS include laminar necrosis of cerebral cortical and hippocampal neurons accompanied by poliomalacia and gliosis[2]. Clinical signs reported in SCS but not noted in these mice include polyuria and polydipsia that may be of neuroendocrine origin[2].

This report emphasizes that background genotype must be considered during knockout and transgenic phenotype analysis. This observation was realized over a decade ago by behavioral neuroscientists; consequently, investigators in this field recommend that knockout mutations be maintained as inbred congenic lines or as F_1 hybrids between two strains. This allows accurate analysis of the phenotype attributable to the transgene alone[5].

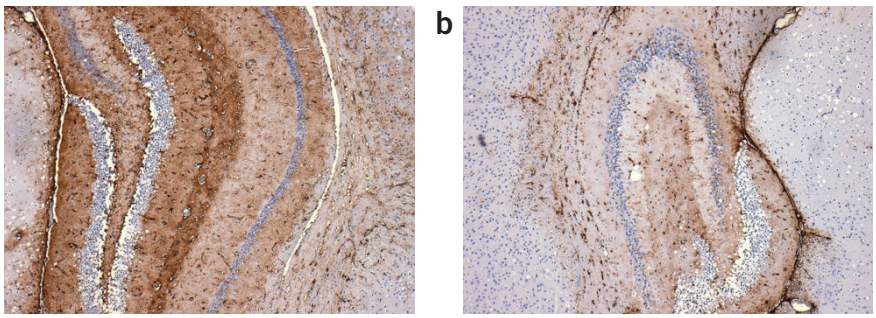

FIGURE 2 | Photomicrographs of the brain taken from two 14-week-old female FVB/n mice found dead with nonspecific gross lesions and no premonitory signs. Both sections are of the hypothalamus. Glial fibrillary acidic protein (GFAP) antibody has been used as an immunostain for glial cells, which stain strongly brown. In (**a**), there is increased labeling for the immunostain (GFAP) most likely from astrocytes filling in the areas of neuronal dropout. It is likely this animal had multiple seizure episodes prior to death that caused ischemic neuronal necrosis and subsequent dropout of neurons. The histopathological appearance of the brain in this mouse is consistent with lesions associated with status epilepticus in humans. In contrast, (**b**) shows immunohistochemical labeling for GFAP within the normal range, indicative of a normal number of neuroglia and suggesting that this animal most likely experienced a single acute and fatal epileptic episode. (Hematoxylin counterstain; low-medium (**a**) and low (**b**) power magnification.)

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