ORIGINAL ARTICLE

Bilateral Agenesis of the Hippocampal Dentate Gyrus in a Neurologically Normal Adult

Arthur W. Clark, Harvey B. Sarnat

ABSTRACT: ***Background:*** Ontogenic development of granule cells in the hippocampal dentate gyrus is influenced by genes including WNT3, EMX2, NEUROD, and LEF1. Dentate granule cells continue to be generated from stem cell precursors postnatally and during adult life, and are implicated in normal and abnormal neurological function. Developmental privation of dentate granule cells is rare and essentially always occurs in the context of other neurodevelopmental abnormalities. We have found no previous reports of severe, selective agenesis of dentate granule cells in humans. ***Methods:*** A gross and microscopic examination of the brain included appropriate histochemical and immunohistochemical preparations and examination of the hippocampal formation at multiple levels bilaterally. ***Results:*** This neurologically normal 82-year-old man was found to have bilateral agenesis of the hippocampal dentate gyrus, no identifiable dentate granule cells, and moderate disorganization of the pyramidal cell layer of Ammon's horn. We found no neurodevelopmental abnormalities outside the hippocampus. ***Conclusions:*** The hippocampal architectural alterations in this patient are similar to those associated with a murine Lef1 mutation, but our human case does not have the other congenital deficits reported in the Lef1-null mouse. Bilateral agenesis of the hippocampal dentate gyrus, and apparent failure of regeneration of dentate granule cells from stem cells in adult life, may occur without overt clinical neurological deficits.

RÉSUMÉ: Agénésie bilatérale du corps godronné de l'hippocampe chez un adulte normal au point de vue neurologique. ***Contexte :*** L'ontogenèse des cellules étoilées du corps godronné de l'hippocampe est influencée par certains gènes dont WNT3, EMX2, NEUROD et LEF1. Des cellules étoilées du corps godronné continuent d'être produites à partir de cellules souches précurseurs après la naissance de même qu'à l'âge adulte. Elles sont impliquées dans le fonctionnement neurologique normal et anormal. L'absence de développement des cellules étoilées du corps godronné est rare et survient toujours dans le contexte d'autres anomalies neurodéveloppementales. À notre connaissance, il n'existe pas de publication portant sur l'observation d'une agénésie sélective sévère des cellules étoilées du corps godronné chez l'humain. ***Méthodes :*** Un examen macroscopique et microscopique du cerveau avec préparations histochimiques et immunohistochimiques appropriées et examen bilatéral de l'hippocampe à de multiples niveaux. ***Résultats :*** Il s'agit d'un homme normal au point de vue neurologique chez qui on a constaté une agénésie bilatérale du corps godronné de l'hippocampe, sans cellules étoilées identifiables, ainsi qu'une désorganisation modérée de la couche de cellules pyramidales de la corne d'Ammon. Nous n'avons pas observé d'anomalies neurodéveloppementales ailleurs qu'à l'hippocampe. ***Conclusions :*** Les altérations architecturales de l'hippocampe chez ce patient sont semblables à celles observées chez un modèle murin de mutation du gène LEF1. Cependant, notre patient n'a pas les autres déficits congénitaux rapportés chez la souris LEF1-nul. L'agénésie bilatérale du corps godronné de l'hippocampe et l'absence de régénération des cellules étoilées du corps godronné à partir de cellules souches à l'âge adulte peuvent survenir sans déficit neurologique évident.

Can. J. Neurol. Sci. 2006; 33: 296-301

Granule cells of the dentate gyrus receive the primary input of neural activity to hippocampus, through the perforant path from entorhinal cortex.[1] Dentate granule cells have been the focus of intense interest because of their possible involvement in mood disorders,[2,3] epilepsy,[4,5] and memory.[6-9] They are exceptional among neurons, in that they are generated throughout life in mammals including humans.[10] This cell proliferation is inhibited by adrenal steroids and by stress.[11]

What effect a severe but selective congenital absence of granule cells might have in humans is unknown. A search of recent literature, and inquiries with professional colleagues, yielded no previous reports or encounters of such an anomaly. The findings to be reported here indicate a failure of neuronogenesis of the dentate granule cells in fetal life, and no evidence of compensatory generation of dentate granule cells in postnatal life, in a man whose neurologic condition was essentially normal.

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Received February 8, 2006. Accepted in final form May 1, 2006.

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Case Report

This 82-year-old man had been active well into his final years. He was the product of a physician-assisted delivery at home. There are no known problems associated with the birth or delivery, but details are lacking. He had an eighth grade education. In his youth, he had worked as a farmer and had suffered a fall with a hip injury, treated with "cortisone shots." He served in an anti-aircraft unit during World War II, and subsequently experienced severe hearing loss. He worked as a barber for 25 years.

A widower, he had a daughter, his only child, who has had epilepsy. This began with a grand mal seizure when she was 29 years old. She was successfully treated with anticonvulsants and was essentially free of seizures between the ages of 40 and 50 years of age but then had a series of complex partial seizures. An electroencephalogram (EEG) showed right temporal slowing; a subsequent sleep deprived EEG showed a focal right frontal dysrhythmia. At 51 years-of-age she underwent magnetic resonance imaging (MRI) which was normal; the temporal lobes and hippocampal structures were symmetric and had normal volume and signal.

In the year following the death of his first wife, the patient may have had several "staring spells" but there is no history of such spells in his later years; no history of seizures during the first 50 years of his life; and no history of having been evaluated or treated for seizures at any time. Except for his daughter, there is no family history of seizures or epilepsy.

The patient was the middle child of five siblings, including an older sister who had died of "flu" at an early age. A younger brother was a talented musician, married and working well into later life, who may have had sufficient depression to require medication; but details are lacking. An older brother was a "loner," may have suffered strokes in later life, and is currently in a nursing home.

Ten years before his death, the patient met the woman who became his common law spouse. He was very active in various organizations. He sometimes did small carpentry work, including wooden puzzles and frames for pictures. He was described by a family physician as "sharp as a tack." His common law spouse reported that he had a lively sense of humor, and that he went bowling, danced, and played cards regularly; and did his own banking even in the last years of his life.

He developed a series of medical problems including chronic obstructive pulmonary disease, congestive heart failure, chronic atrial fibrillation, hypothyroidism, chronic renal failure, coronary artery disease, myocardial infarction, severe left ventricular dysfunction and mitral valve regurgitation. He had a surgical procedure in the 1950s for peptic ulcer disease. Terminally, he suffered increasing cardiopulmonary problems, which led to his death. Imaging of the brain had never been performed for lack of clinical indication.

Although a poorly documented "dementia" was included in his list of problems in late life, examination of the clinical records and an interview with the common law spouse failed to substantiate this. His hearing deficit may have been the reason for his occasional inability to give an adequate history.

The general autopsy confirmed an extensive organizing pneumonia, severe atherosclerotic cardiovascular disease, small finely granular kidneys, and a colloid cyst of the thyroid. There was mild autolytic change in the adrenal glands, which were otherwise histologically unremarkable.

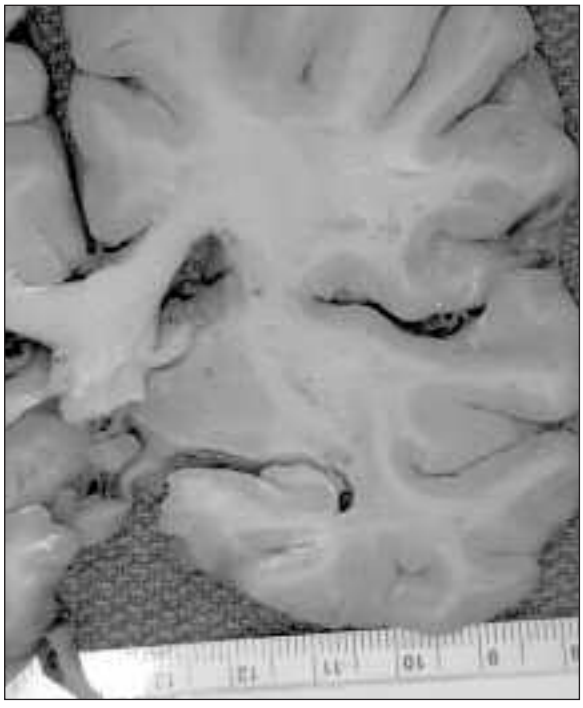

Figure 1: *In coronal sections the hippocampal formation was slightly reduced in size. The hippocampal sulcus was more prominent than usual in this coronal plane of section.*

Neuropathologic findings

The gross brain weight was 1336 grams. The brain was initially interpreted as normal to gross examination except for a slightly atrophic appearance of the unci, associated with a slightly reduced size of the hippocampal formations bilaterally. The brain was examined in coronal sections. The ventricles were of normal size, including the temporal horns. In retrospect, the hippocampal sulcus was more extensive than usual (Figure 1). The cingulate gyri, fornices, anterior commissure, and mammillary bodies were grossly normal in size and configuration as were the cerebellum and brainstem. Sections taken for histologic examination included the left hippocampus at four anterior-posterior levels and the right hippocampus at two levels, including the level of the lateral geniculate body for both left and right sides. Additionally, the left and right amygdalae were sampled for histology.

Microscopic examination of the hippocampi bilaterally revealed agenesis of the dentate gyrus; the hippocampal sulcus was more extensive and prominent than normal (Figure 2; compare with normal control, Figure 3). No dentate granule cells were identified. Morphologic features of the most tightly packed neurons were consistent with pyramidal cells rather than granule cells (Figure 4; compare with normal control, Figure 5). An

https://doi.org/10.1017/S0317167100005163 Published online by Cambridge University Press

Figure 2: *Hippocampal formation in the patient of this report, taken in the coronal plane at the level of the lateral geniculate body. Agenesis of the dentate granule cell layer and dispersion of the pyramidal cell layer, which lacks the normal compaction of CA2 and CA3, are readily apparent when compared with Figure 2. (Nissl stain, 18X)*

Figure 3: *Normal control hippocampal formation from a 71 year old adult, in the coronal plane of the lateral geniculate body. (Nissl stain, 18X)*

occasional cluster of small neurons, possibly representing dentate granule cells, could be identified in some sections, but even under the assumption that these were dentate granule neurons, the dentate granule cell population was less than 5% of the normal. Although the pyramidal cell layer of the hippocampus was well populated, it was aberrantly organized, with dispersion of the pyramidal cells in CA3 and CA2 and a terminal sector which presumably corresponded to CA4 (hilar) neurons. GFAP immunohistochemistry showed subpial reactivity adjacent to the hippocampal sulcus, and subependymal reactivity around the alveus, but essentially no reactive gliosis. Luxol fast blue stains confirmed an essentially normal configuration of the alveus and, in the parahippocampal gyrus, of the subcortical white matter.

No convincing dysgenesis of other structures in cortex, brainstem, or cerebellum was identified. The subiculum and parahippocampal gyrus had essentially normal anatomic features bilaterally. The cerebellar granule cells appeared normal in number and distribution (Figure 6). The mesencephalic nucleus of the trigeminal nerve was also identified and appeared qualitatively normal. There were age related changes including numerous senile plaques in cortex, evident on Bielschowsky silver staining. Neurofibrillary tangles, found in the hippocampus and parahippocampal gyrus, did not exceed the numbers commonly seen among elderly non-demented subjects, and there was no evidence of Alzheimer's disease or other

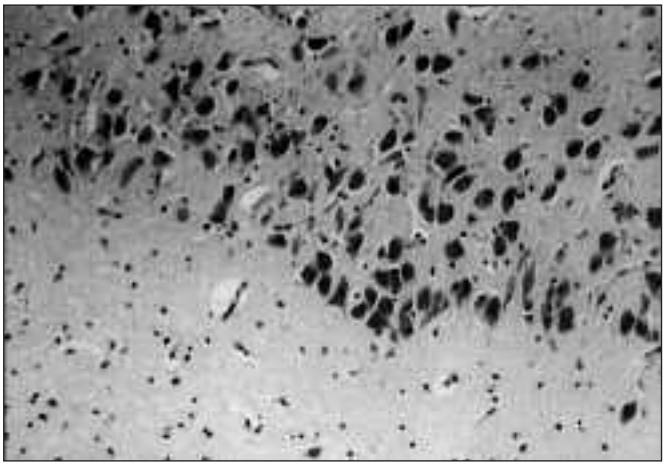

Figure 4: *Pyramidal cell layer of the hippocampus in the patient of this report, at the point of maximum cell packing density. (Nissl stain, 140X)*

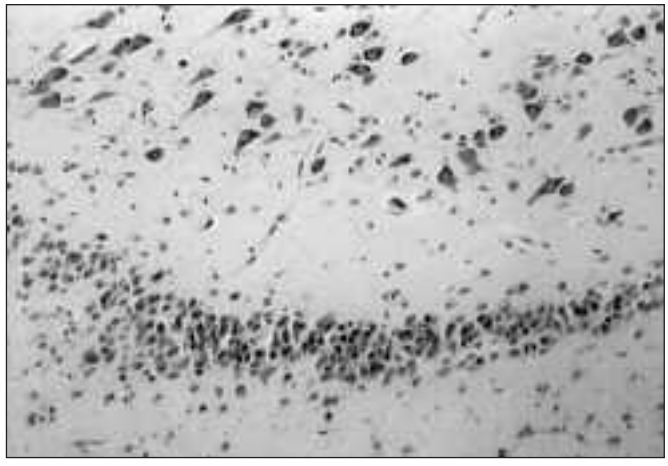

Figure 5: *Normal control dentate granule cell layer and CA4 of the hippocampal formation, for comparison with Figure 4. (Nissl stain, 140X)*

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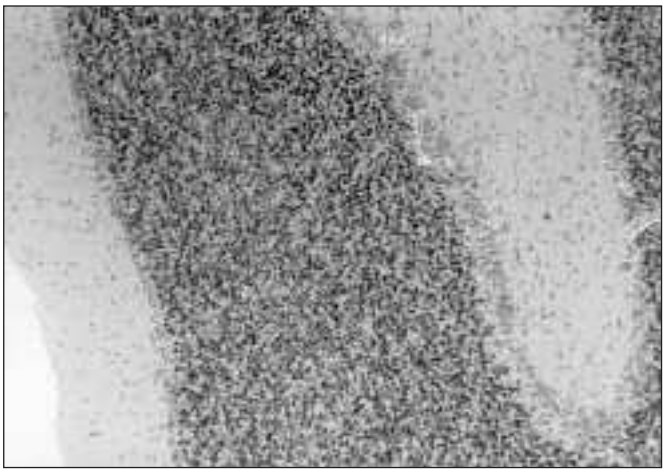

Figure 6: *Cerebellar cortex in the patient of this report, showing normal anatomy (Hematoxylin-eosin stain, 70X)*

primary neurodegenerative disorder. An old cavitating microinfarct was found in the left occipital lobe, and a reduced volume of the anterior pituitary suggestive of the empty sella syndrome.

Discussion

Our findings document agenesis of the dentate gyrus, and severe privation or total absence of its granule cells, in a neurologically and psychologically healthy adult. The moderate but definite abnormalities in architecture of the hippocampal pyramidal cells; the absence of reactive gliosis; and the finding of extension and increased prominence of the hippocampal sulcus, all provide evidence that the abnormalities are the result of agenesis rather than a postnatal degeneration of dentate granule cells. We cannot exclude the possibility that some clusters of small neurons found in the sections might have been aberrantly positioned dentate granule cells or their progenitors. However, we found no convincing evidence for this in the sections taken from multiple levels of hippocampus bilaterally.

On the basis of the anatomic findings as well as the clinical history we can therefore exclude such postnatal effects on dentate granule cells as have been described for colchicine toxicity,[12] adrenalectomy,[8,13] trimethyl tin,[14] hypoglycaemia,[15] or a familial syndrome with congenital cataract and dementia.[16]

The severe privation or absence of hippocampal granule cells in this case is probably the result of two distinct aberrations: 1) defective initial neuronogenesis of these specific neurons in fetal life, and 2) failure of postnatal and adult neuronogenesis (by the recruitment of stem cells in the subdentate zone) to compensate for the original deficit.

Developmental abnormalities of the dentate gyrus as extensive as the one reported here are rare in humans, and generally are associated with more widespread dysgenesis.[17,18] A more selective defect in fetal neurogenesis of granule cells occurs in some cases of infants with selective congenital granuloprival cerebellar hypoplasia, associated with absence of hippocampal granule cells of the dentate gyrus, without reactive gliosis.[17,19] We found no abnormality of cerebellar granule cells in the case reported here.

Granule cells of both the fetal hippocampus and the cerebellum begin to form in the 13th week of gestation in humans, with rapid proliferation of the medial hippocampal layer and the external granular layer of the cerebellum during the fourth fetal month.[20-23] Dentate granule cell neurogenesis and migration in the mouse brain have also been well studied.[24,25]

As with olfactory bulb granular neurons, neurogenesis of dentate granule cells occurs throughout life in mammals, including humans.[2,10,24-30] New neurons are continuously generated in the subventricular zone of the lateral ventricles and in the subgranular zone of the dentate gyrus. Our findings indicate a failure of postnatal neurogenesis for the dentate granule cells. Although the olfactory tracts were present on gross examination of the brain in this case, the olfactory bulbs were lost in post-mortem handling of the tissue, and we are unable to document the histology of the olfactory bulbs.

Several genes are involved in development of the dentate granule cell layer; and engineered mutations in some of these genes have been associated with agenesis or aberrant development of the dentate gyrus. But each of these mutants has far more widespread developmental defects than an isolated agenesis of the hippocampal dentate gyrus.

The WNT3 gene, located on chromosome 17 in humans and chromosome 11 in mice, appears to be one of the principal neurogenic genes in the mouse, not only for initial fetal development of this structure but also for a turnover and replacement of dentate gyral neurons from activated stem cells in adult life.[31,32]

The NEUROD gene is located on chromosome 2 in both humans and in mice, is essential for normal development of many types of neurons, as well as of pancreatic beta cells; a null mutant in mice is lethal because of diabetic complications. Mutant mice rescued from the diabetes develop a severe hypoplasia of granule cells in both the cerebellar cortex and the hippocampal dentate gyrus.[33] However, the defect appears to arise relatively late in development of these structures; aberrant architecture of the hippocampal pyramidal cells, such as that seen in our case, has not been demonstrated.

The EMX2 gene is located on chromosome 10 in humans and chromosome 19 in mice.[34,35] A null mutant in mice is associated with severe urogenital agenesis and death within a few hours after birth. In the brain, agenesis of the dentate gyrus has been attributed to marked reduction of the glial scaffolding and consequent arrest in migration and maturation of dentate granule cell precursors.[36] These mice have other neurodevelopmental anomalies including reduction in size of Ammon's horn, the fimbria and fornix, and the cingulate cortex area.[37]

The LEF1 gene is located on chromosome 4 in humans and chromosome 3 in mice.[38,39] In a mouse homozygous for a null Lef1 allele, the dentate granule layer fails to develop, and the hippocampal pyramidal cell layer is aberrant, in a pattern remarkably similar to the hippocampal anatomy in the case reported here.[40] But the same Lef1 mutant mouse also fails to develop the mesencephalic nucleus of the trigeminal nerve. In fact, this mutant has severe somatic abnormalities and dies not long after birth.[38] None of these mutant mouse models remotely

approximates normal development outside the hippocampal dentate gyrus.

In addition to the genes crucial to dentate gyral development, basic fibroblast growth factor and ciliary neurotrophic factor also are important for maintenance of the stem cell pool and self-renewal of neural precursors, under the control of Notch signalling.[41,42] Brain-derived neurotrophic factor levels increase with physical exercise (wheel running) in normal mice, probably secondary to activation of NMDA receptors in the hippocampus with enhanced neurogenesis, but this phenomenon does not occur in brain-derived neurotrophic factor knockout mice.[43] Neurotransmitters, including norepinephrine, acetylcholine and glutamic acid, also play roles in promoting dentate granule cell neurogenesis from stem cells.[43-47]

From previously available reports, it is very difficult to predict what neurologic effects a selective absence of or damage to dentate granule cells might have in humans. The hippocampal formation is essential to normal learning and memory;[48] but much less information is available on a possible specific role for the dentate gyrus.[9,49] In epilepsy, the dentate granule cells are believed to serve as a barrier to epileptic activity provided their normal circuitry is preserved.[4,5,50] Early and persistent failure of dentate granule cell neurogenesis might be a cause or an effect of mood disorders.[11]

Agenesis of even so prominent a structure as the corpus callosum may be compatible with essentially normal neurologic function, requiring specific neurologic testing to detect any related deficit. Callosal agenesis may be regarded as a primary disorder of axonal projection, however, not of neuronogenesis. The small pyramidal cells of layer 3 of the cerebral cortex are preserved, but their axonal trajectories find aberrant pathway in the anterior commissure, bundle of Probst, internal capsule and ventral corticospinal tract and other sites.[51]

The fact that the individual described in this report had no obvious mood disorder or learning handicap does not rule out the possibility of subtle specific subclinical deficits in neurologic function. Reorganization of synaptic circuitry might have compensated for the absence of dentate granule cells. Selective loss of dentate granule cells occurring later in life might produce a very different outcome.

The cause of the developmental abnormality reported here remains unproven, but almost certainly affected very early stages of development of the dentate granule cells. If it is due to a genetic defect, the effects are more isolated and specific than for any genetic mutation yet reported involving dentate granule cell development. Our finding, that severe hypoplasia or congenital absence of the dentate granule cells produces no overt neurologic deficit in humans, is important information for understanding normal brain function.

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