Dendritic Spine Pathology in Infants With Severe Protein-Calorie Malnutrition

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ABSTRACT. *Background.* **Experimental undernutrition in animals, during the critical brain development period, produces retardation of brain growth as well as a number of different morphologic and functional abnormalities in neurons, mainly in the dendritic synaptic apparatus. These alterations are the cause of the poor neurointegrative development that occurs in experimental malnutrition. Severe malnutrition during early postnatal life in humans is known to produce similar neurointegrative disorders as well as mental retardation, but there are very few studies describing the morphology of the dendritic apparatus in infants suffering from this condition.**

Objective. **To study the dendritic spine density and morphology in dendrites from cortical neurons in infants dying from severe malnutrition.**

Methodology. **Brain sections from the somestesic, motor, and occipital cortical areas of 13 infants who died of severe malnutrition and 7 eutrophic infants who died of other causes were studied by means of the rapid Golgi method. Apical dendritic spines from neurons of the fifth cortical layer were studied and counted in all sections.**

Results. **Apical dendrites were significantly shorter in malnourished infants than in the control group (581.54 ± 54.32 μm in severe malnutrition vs 846.3 μm in normal infants). The number of dendritic spines per dendrite was also significantly diminished (185.3 ± 36.1 in malnourished vs 374.3 ± 41.6 in eutrophic infants). There were marked morphologic abnormalities in the dendritic spines of infants dying of severe malnutrition that were classified as dysplastic.**

Conclusions. **Short apical dendrites, fewer spines, and dendritic spine abnormalities occur in severe infant malnutrition. These anatomic anomalies might be related to the neuropsychological deficits that occur in these children.** *Pediatrics* **1999;104(2). URL: http://www. pediatrics.org/cgi/content/full/104/2/e21;** *dendrites, dendrite spines, malnutrition.*

ABBREVIATIONS. MI, malnourished infants; NI, normal infants.

Undernutrition during early postnatal life produces a significant slowdown in the rate of central nervous system growth,[1,2] with lower brain weight,[3] thinner cerebral cortex,[4] diminished number of neurons,[5] deficient myelination,[6] poor dendritic arborization, and several changes in the microscopic features of spines such as a reduction in their width and number.[7–11] Although dendritic spines were described over a century ago, their role in neuronal function is still a matter of intensive study. It is known that the density of spines increases as the neuron develops and that they vary in size, number, and shape as a function of the history of the neuron, and that they degenerate in aged neurons.

Recently, several morphologic studies have set forth the importance of dendritic spines in different pathologic conditions in humans and in protein-calorie malnutrition in laboratory animals. Of particular interest are those studies that correlate mental retardation with or without chromosomal abnormalities, with an altered number, distribution, and aberrant morphology of dendritic spines.[12–15] Some authors have correlated these abnormalities with poor behavioral and psychological development, inadequate auditive and visual integrative development, and a remarkable reduction in intellectual coefficient and attention.[9,14,16,17] But so far, there are no systematic studies concerning dendritic spine pathology in malnourished infants during the critical postnatal brain development period. It is known that infants suffering from severe nutritional deprivation during early postnatal life show neurointegrative disorders and various degrees of mental retardation that might persist for years after recovery.[18–20] Conceivably these altered higher brain functions could be attributable in part to a deficient development of the dendritic spine apparatus. The main purpose of this investigation was to study the distribution and morphology of dendritic spines in the brain cortex of children dying from severe malnutrition during the early postnatal life.

METHODS

Cases were selected from the pathology department of the Hospital Infantil Federico Gómez (Mexico City) with the following criteria: a) diagnosis of severe protein-calorie malnutrition, with a body weight loss of 30% or more; b) a time after death of no longer than 12 hours and body kept in refrigeration; c) no clinical or autopsy diagnosis of any meningeal or brain pathology (meningitis, encephalitis etc); d) macroscopically well-preserved brain tissue; e) absence of congenital anomalies, and f) age below 24 months. Thirteen cases of both sexes whose ages ranged from 8 to

24 months were finally included in our study. Seven controls were selected from infant deaths arriving at the pathology department of the aforementioned hospital with the following criteria: a) eutrophic infants of normal weight; b) age matched (8–24 months of age); c) no meningeal or brain pathology; d) no congenital anomaly; e) well-preserved brain tissue, and f) no more than 12 hours postmortem. (All autopsies were performed after obtaining written permission for a complete postmortem including brain).

Sections from the somestesic, motor, and occipital areas from freshly obtained brains measuring approximately 1 cm³ were processed with the rapid Golgi silver chromate method (Ramón y Cajal and de Castro) as modified by Marín-Padilla.[21,22] All procedures were performed in the dark. Stained blocks were then dehydrated in the routine alcohol-xylene series and embedded in low-melting paraffin. Blocks were cut in a sliding microtome at 150 to 200 μm, deparaffinized in xylene and soaked in clove oil for 20 to 30 minutes for clearing. Sections were put on slides and covered in Damar resin with cover slides. Microscopic examination was performed on a Reichert Young Polyvar transmitted light microscope with the aid of an optical grid (1.0 μm) for measurements.

Microscopy

Neurons from the fifth cortical layer were selected only if they were well-impregnated and had long apical dendrites. Ten pyramidal cells from each cortical area sampled were studied. The dendrite was followed from the emergence of the neuron to the first bifurcation at the second cortical layer. The length of the dendrite was measured focusing segments of about 100 μm and the amount of branching was estimated (not counted). Dendritic spines were counted at 50 μm intervals beginning at the emergence of cell body to the first bifurcation of the dendrite.

In all, 130 dendrites from the cases and 70 from controls were measured in each cortical area, and dendritic spines were counted along each dendrite. Dendritic measurements and dendritic spine counts were performed independently by two of the authors (L.B.B. and I.D.A.). The variability was between 9% and 16%. The mean of the two counts was used for statistical analysis (Student's t test). Dendritic spine morphology was studied and photographed on high-contrast film to avoid background and to highlight shape.

RESULTS

The anatomic differences of the apical dendrites in malnourished infants (MI) and the control group of normal infants (NI) were striking in the three cortical areas studied. The average length of the apical dendrites was 846.43 μm $\pm$ 46.09 in NI, whereas in MI the average was 581.54 μm $\pm$ 54.32 ($P <$ .001) (Fig 1). The number of spines per dendrite in NI was 347.3 μm $\pm$ 41.6, while in MI, it was 185.3 μm $\pm$ 36.1 ($P <$ .001) (Fig 2). Dendritic spine counts in each cortical area studied also showed marked differences. The motor area in NI was 345 μm $\pm$ 26.8 in NI vs 183.7 μm $\pm$ 29.4 in MI ($P <$ .001); in the somestesic area, 372.7 μm $\pm$ 36.5 in NI vs 180.7 μm $\pm$ 44.6 in MI ($P <$ .001); and in the occipital area, 323.9 μm $\pm$ 44.5 in NI vs 191.4 μm $\pm$ 31.7 in MI ($P <$ .001). The distribution of the apical spines was also quite different. Along the first 250 μm from the neuronal body, the number of spines was similar in both groups. In contrast, in the distal segment, there was a significant reduction in all the cortical samples from the undernourished group (Fig 3). Moreover, taking into account an equivalent proportion of distal segments, it was evident that the lower number of spines counted was not dependent on the shorter length of the dendrite found in MI. There were also some dendritic segments denuded of spines.

The morphology of spines showed remarkable changes mainly in the distal portion of the dendrite. Some had long stems, others were clubbed, and even others shared fused and curled stems (Fig 4). We applied the term dysplastic spines to describe these abnormal dendritic processes instead of using the alternative term dysgenic spines, previously applied by Púrpura[13] to the abnormal dendritic morphology reported in other types of mental retardation. The term dysplastic seems more appropriate for naming the abnormal morphology found in these spines, because it refers to altered formation and not to a deranged genetic program. This study demonstrates
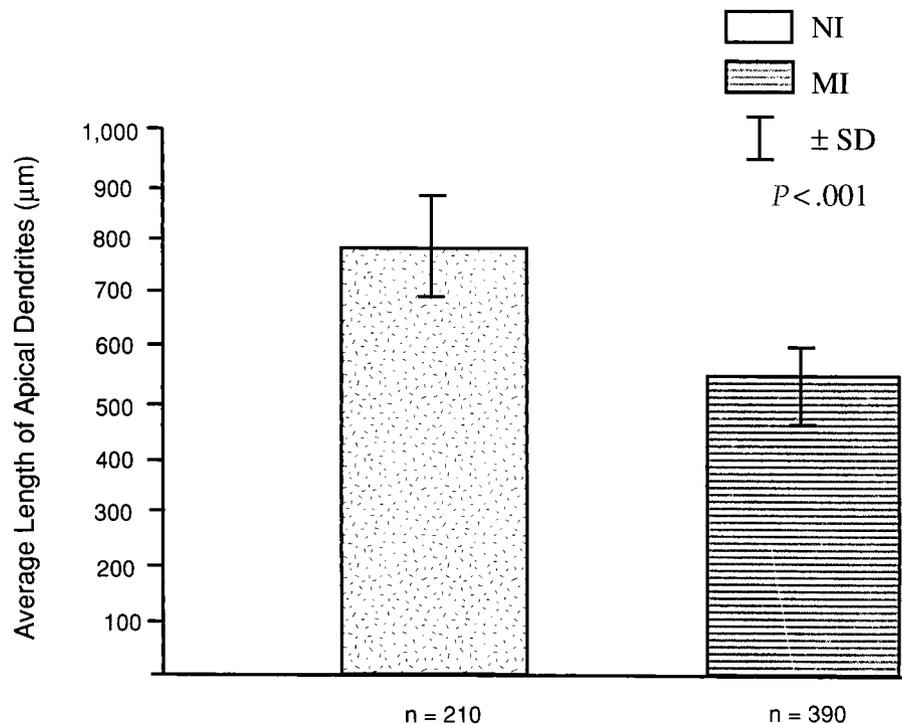

Fig 1. Average length of apical dendrites of neurons from the fifth cortical layer in all areas studied. NI indicates normal infants; MI, malnourished infants.
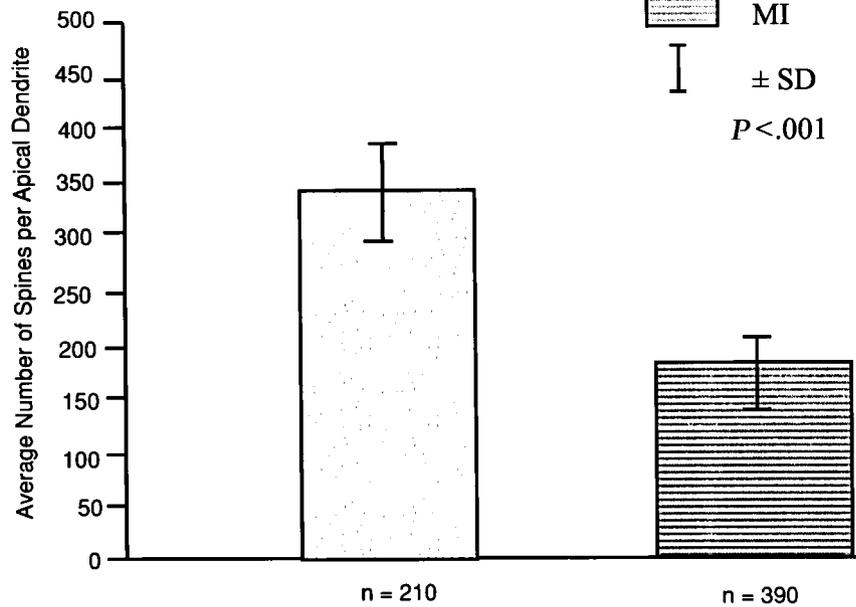
Fig 2. Comparison of the number of spines per apical dendrite of the pyramidal neurons from the fifth cortical layer, between NI and MI. Bars represent the mean ± SD from counts performed on cortical samples of motor, somestesic, and occipital areas.
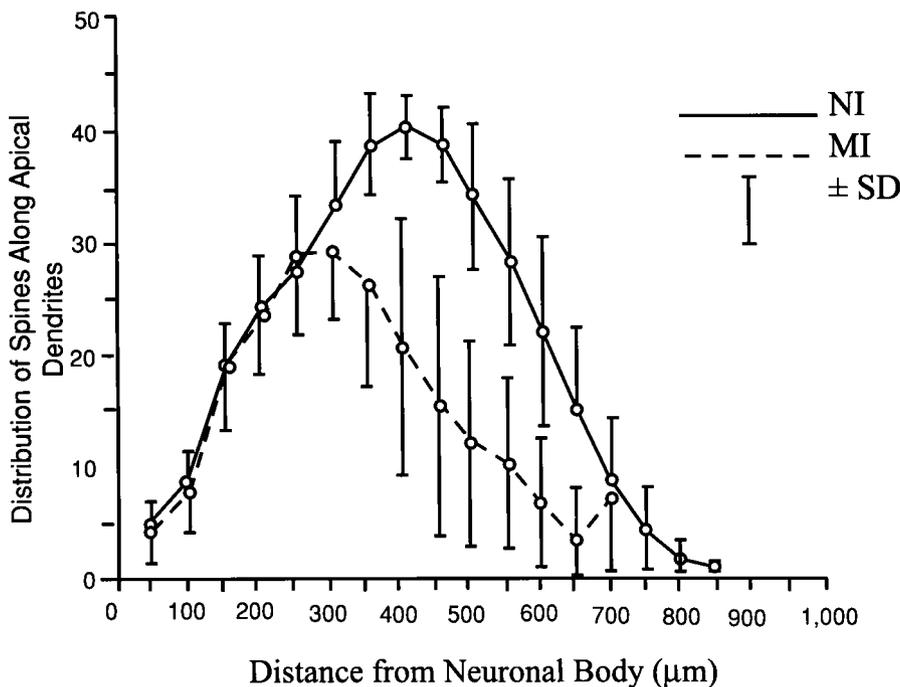

Fig 3. Differences in dendritic spine density between the proximal and distal portion of the apical dendrites in the motor area. Note that the proximal segment has a similar number of dendritic spines in both groups, while in the distal portion there is a significant reduction of spines in MI. Other cortical areas displayed a similar distribution pattern. NI indicates normal infants.

the following three specific and different kinds of dendritic abnormalities in children who died from severe protein-calorie malnutrition: 1) shortening of the apical dendrite; 2) a decreased number of dendritic spines in the distal half; and 3) presence of abnormal or dysplastic spines.

DISCUSSION

Our results show that in early protein calorie-malnutrition during the critical brain development period (first 24 months of age), there are severe alterations in the dendritic spine apparatus of neurons from the fifth cortical layer. The changes comprise a shortening of the apical dendrite, a significant decrement of the number of spines and the presence of abnormal forms that we have defined as dysplastic spines. These abnormalities were in the proximal 250 μm of the dendrite, but in the distal portion they were particularly striking. It is known that the development and arborization of apical dendrites from the brain cortex continues to progress postnatally and is completed around the second year of age. It is therefore likely that the proximal portion of the dendrite and the corresponding spines developed before the onset of nutritional deprivation, probably in fetal life, but that the distal portion developed later when the lack of appropriate nutrition interfered with normal growth. Numerous experimental studies in
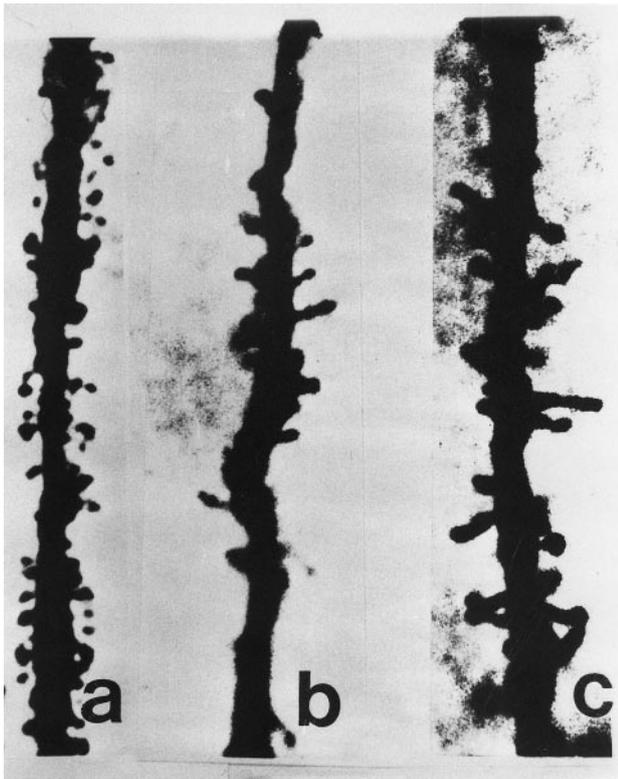
Fig 4. Photomicrographs of equivalent segments of apical dendrites at ~400 μm from the neuronal body. A indicates a eutrophic infant showing regularly distributed and morphologic normal dendritic spines; B indicates MI with large portions of the dendrite devoid of dendritic spines. The few spines present are clearly dysplastic; and C, MI with dysplastic spines. Some are elongated, others are clubbed, and some others are fused; and the distribution is irregular (rapid Golgi method, enlarged from 600× in high contrast film).

mammals have shown that protein calorie deprivation produces similar changes in the dendritic-synaptic apparatus when induced during the critical development period of the brain cortex.[8–11] Dobbing and Sands[4] showed diminished dendritic arborizations of neurons of the fifth cortical layer in experimental animals with nutritional deprivation. Salas et al[23] found thinner dendrites and diminished spine numbers in neurons from the occipital cortex. Díaz-Cintra et al[24] have demonstrated the effects of parenteral protein deprivation on the postnatal development of granular cells in fascia dentata.

The abnormalities of the dendritic apparatus in humans have been described mainly in mental retardation, chromosomal abnormalities and in senile dementia, but not in severe malnutrition. Marín-Padilla[12,14,15] found severe abnormalities in the cerebral cortex, principally of the axospinodendritic synapsis, in human chromosomal aberrations, and Púrpura described dendritic spine dysgenesis in mental retardation without chromosomal anomalies.[13] Previous investigations in experimental animals show that severe protein calorie malnutrition during the first stages of postnatal life produces remarkable changes in the development of the cortical dendritic apparatus.[8,9,20,23] Early undernutrition may also produce functional abnormalities in the central nervous system, because the development of neuro-

nal interconnections appears to be retarded.[24–27] There are a number of anatomic studies that provide information on the structural basis of these alterations: Cragg[8] in 1972 reported a retarded neuropil development; Cordero et al[10] in 1985 found a decreased dendritic arborization, and Gambetti et al[28] in 1974 showed a decrease in the size and density of the presynaptic endings. Other studies in experimental animals, mainly in the developing rat, demonstrate that in protein-calorie malnutrition, the number of dendritic spines in the cerebral cortex, including the dentate gyrus, is clearly diminished.[23,24] Although the functional significance of these abnormalities remains unclear, it is reasonable to suggest that they could produce deleterious effects on brain plasticity, and as a result, they may involve integrative function.[29]

The dendritic spine is a dynamic structure, highly responsive to environmental changes. It is known that spine development and its maturation are characteristically sensitive indicators of the developmental stage of a given brain area. For instance, in humans, distal dendrites and their spines develop later in language areas than in motor cortex.[30] Shepherd[31] in 1990 postulated that the spine is the smallest neuronal compartment capable of performing a complete input-output operation of a single synapse. This implies that spines not only create a site for synaptic connection, but that they also give rise to structural, biochemical, and physiologic areas, specific for an individual compartment. Therefore, this structure as well as being a specific target for particular synaptic inputs, functions as a dendritic growth cone, probably stimulated by the action of astrocytes.[32] Dendritic spines are also related to three important functions: a) long-term potentiation phenomenon that requires an increase in intracellular calcium; b) modulation of calcium dynamics, and c) amplification of synaptic input signals. All these facts support the idea that changes of density and morphology in spines and their synapses may be involved in mental disorders such as neurosis or even psychosis.[31] They also suggest that subtle spine changes could be related to abnormal behavioral and cognitive function.[33,34] In fact, dendritic spine anomalies are a common feature in the brain cortex of profound mental retardation without chromosomal abnormalities.[13] In contrast, in Down syndrome a diminished number of spines together with some abnormal features, such as long and thin stalks in dendrites, from neurons of the cerebral cortex have been described.[15] Similarly, fragile X syndrome, and presenile and senile dementia show dendritic abnormalities,[35,36] although the number of spines is increased.

In experimental fragile X syndrome in knockout mice lacking the Fmr1 gene, dendritic spine abnormalities consist of longer and thinner stalks in the apical portion of dendrites of the pyramidal neurons of the fifth cortical layer from the occipital cortex.[37] This syndrome seems to be the consequence of the lack of the fragile X mental retardation protein, which is necessary for normal spine development.

Our observations revealed pathologic dendritic

spine changes associated with early malnutrition, similar to those described in mental retardation of different causes. Although it is difficult at present to demonstrate that spine pathology is the cause rather than a coincidental relationship with mental retardation, it is tempting to assume that these morphologic changes could represent, at least partially, the structural basis of the synaptic dysfunction associated with early severe malnutrition.[38,39] Hence, the severe neurointegrative disorders described in malnourished infants could be a consequence of the abnormalities in the dendritic (synaptic) apparatus described in this study.

Under normal conditions, spines are able to regulate calcium interstitial levels, avoiding the sudden influx of this ion into neighboring dendrites, which could be extremely toxic. In fact, this abnormality especially in the distal segments produces an inability to manage relatively high and sudden increments in intracellular calcium concentrations, leading to the inhibition of neuronal plasticity, and eventually to neurolysis.[40,41] Dysplastic spines might also be dysfunctional and could thus trigger the destruction of parent dendrites.

It is also interesting to point out that neurons from different areas in the central nervous system do not respond equally to the same kind of malnutrition. For instance, Andrade et al[42] in 1995 demonstrated that under long-term protein deprivation, CA3 pyramidal neurons, principally fiber-CA3 synapses, and dendritic trees of the dentate granular cells show a remarkable decrease in the total number of dendritic arborizations per cell, as well as loss of spines, without evidence of regrowth. In contrast, other authors under similar conditions describe that neither the dendritic features nor the number of spines undergo any change.[31] Nevertheless, Cadete-Leite et al[43,44] have demonstrated that neurons in the dentate gyrus have the capability to increase the number of their dendritic segments, as a compensatory response of the surviving neurons to the death of their close neighbors. Supporting this observation, Horner[45] in 1993 observed that lengthy periods of a low-protein diet produce an increment in spine density around the proximal and distal segment of dendrites, markedly increasing the area of synaptic contacts. But if we take into account that the total dendritic length of granule cells decreases as a result of protein deprivation, the number of spines per granule cell is not likely to be increased and may even be reduced.[46]

In experimental animals rehabilitation from malnutrition does not lead to an improvement of the morphologic, degenerative, or physiopathologic changes it provokes.[47,48] The timing of onset of protein deprivation is a determining factor of its effects. The maximal vulnerability is during the brain growth spurt period, which takes place in early postnatal life.[4,5] In humans, little is known about the neuropathology of early malnutrition and the associated physiopathologic changes have been studied indirectly.[27] Maternal protein-energy malnutrition does not produce permanent neurologic or intellectual deficit in the fetus because brain growth is unaffected.[49] In the first 24 postnatal months, however,

malnutrition exerts the strongest neurologic damage. Infants undernourished in the postweaning period manifest neurologic and intellectual deficit.[50] The dendritic spine abnormalities described in this study, particularly the diminished density and the presence of dysplastic forms of this structure, are the consequence of a precarious nutritional input and could constitute the anatomic basis of the poor neuropsychologic development that these infants display. It has been shown in some studies that after nutritional rehabilitation, the motor and mental development of undernourished children is equal to that of the control group.[50–52] It is known, however, that after severe undernutrition in the first postnatal months there are certainly irreparable cognitive deficits.[53] So far there are no studies to demonstrate whether the dendritic spine abnormalities associated with severe early malnutrition in humans can be repaired by proper nutritional rehabilitation or whether they persist throughout life.

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