

# ASYMMETRIC BILATERAL MEGALENCEPHALY. A CASE REPORT

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## SUMMARY

We report a necropsic case of asymmetric bilateral megalencephaly due to diffuse gliosis of malformative nature without apparent neuronal changes in a 9 month-old-child. There was also hypotrophy of the lymphoid system but we did not find enough evidence to support a relationship between this finding and the megalencephaly.

## RESUMO

### Megalencefalia bilateral assimétrica — descrição de um caso clínico

Neste trabalho descreve-se um caso necrótico de megalencefalia bilateral assimétrica devida a gliose difusa de natureza malformativa sem alterações neuronais aparentes, numa criança de 9 meses. Existia concomitantemente hipotrofia do sistema linfático embora os autores não tivessem encontrado provas suficientes para estabelecer uma relação definitiva entre este achado e a megalencefalia.

## INTRODUCTION

Megalencephaly is a descriptive umbrella which covers many conditions leading to an increase of size and weight of the brain.<sup>1, 2</sup> This increase can be bilateral (symmetric or asymmetric) or unilateral<sup>3</sup> and may reflect either the enlarged size of brain cells in storage diseases or the increased number of neuronal and/or glial cells in several more or less well defined neurological disorders.<sup>3, 4</sup>

Apley and Symons<sup>4</sup> stressed that in most cases of megalencephaly death was sudden and appeared to be associated with an acute febrile illness. Taking into account that the lymphoid system was deficiently developed in two of the four cases of megalencephaly described by Bartel<sup>5</sup> they advanced, moreover, that this cerebral malformation might be related, at least in certain cases, to an immunologic deficiency.

The purpose of this report is to describe a necropsic case of megalencephaly in which there was some morphological evidence pointing to the abnormality of the lymphoid system.

## CASE REPORT

A 9-month-old white male died 4 hours after admission to *Hospital de S. João* with a clinic diagnosis of meningitis. At birth he weighed 3.000 g, had a head circumference of 35 cm and exhibited respiratory difficulty, cyanosis and hypotonia. After discharge from the *Maternidade Júlio Dinis* he went on being followed in *Hospital Maria Pia* where a retarded psychomotor development was found. At admission to *Hospital de S. João* the infant had a fairly large head (47 cm of circumference) and the anterior fontanelle

measured 2.0 by 2.0 cm; the neurologic examination disclosed hyperreflexia, head hyperextension, spasticity of four limbs, paralytic strabismus and normal optic fundi. The lumbar puncture showed 1.200 cells/mm<sup>3</sup>. There was neither family history of megalencephaly, nor previous history of repeated infections. The karyotype was normal.

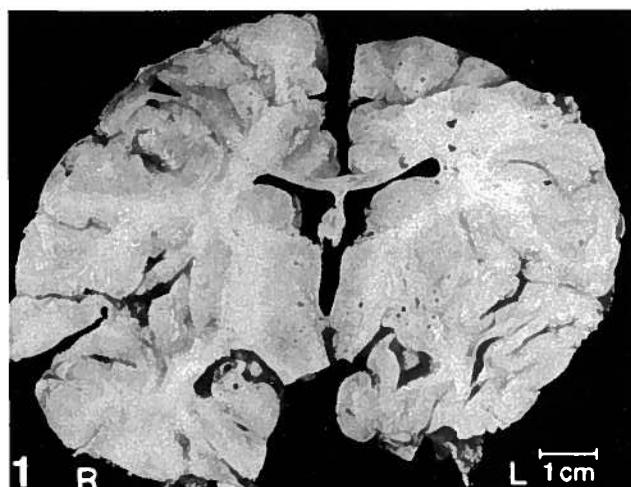


Figure 1: Asymmetrical enlargement of the right parietal and temporal lobes with microgyria (arrow). The left thalamus is smaller than the right.

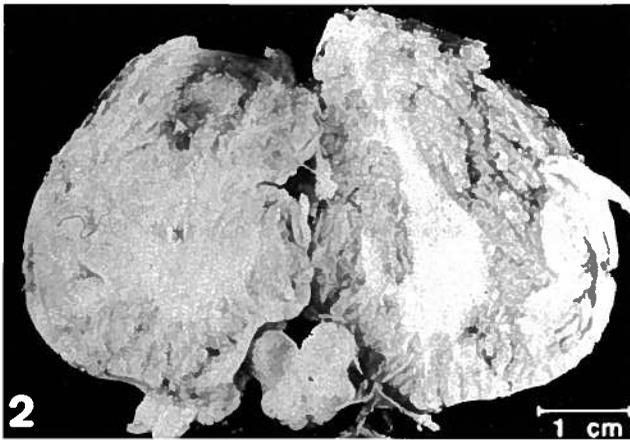


Figure 2: The quantity of grey matter is greater than usual in the cerebellum. The cerebellar hemispheres appear to be of an equal size and the medulla shows no gross abnormalities.

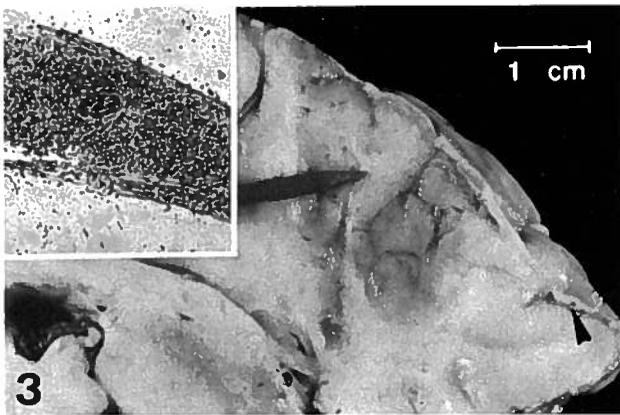


Figure 3: The grey matter throughout the superior part of the frontal lobe is disproportionately greater than the white matter and bulges at the surface section (arrow). The leptomeninges are thicker than usual. Inset: Abundant inflammatory exudate in the leptomeninges without evident alterations of the cerebral cortex: hematoxylin-eosin, (X 40).

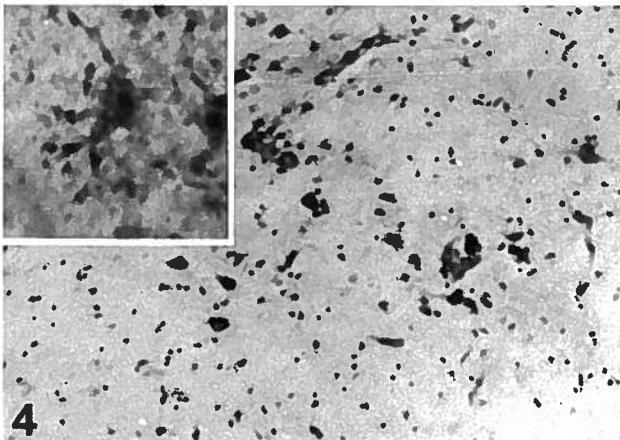


Figure 4: A few neurons are scattered among many neuroglial cells. Toluidine-blue, (X 300). Inset: Most neuroglia elements are microglia cells. Gold sublimate of Cajal, (X 1.200).

## NECROPSIC FINDINGS

Abnormalities were limited to the head with the exception of an overall reduced size of the lymphoid organs. There was not homolateral gigantism. The fresh brain weighed 1.200 g, showed a striking enlargement of cerebral and cerebellar hemispheres and had microgyri on the right parietal lobe (Figures 1 and 2). Leptomeninges were thick, had a cloudy appearance and disclosed fibrinopurulent deposits on the basis and over the convexities of the hemispheres. Marked congestion and small areas of subarachnoid hemorrhage were seen over the hemispheres and brain-stem. Dural sinuses and the hypophysis were normal and a purulent otitis media was found on the side. Coronal sections through the cerebral hemispheres revealed a normal ventricular system and an asymmetrical enlargement of the frontal, parietal and temporal lobes of the right hemisphere (Figure 1). Coronal sections showed, moreover, that both in the forebrain and in the cerebellum the grey matter bulged at the surface section and seemed to be much larger and softer than the usual (Figures 1, 2 and 3). Basal ganglia had a normal appearance but the left thalamus was smaller than the right (Figure 1).

At the histological level the meninges had striking inflammatory exudate (Figure 3 inset) and the white matter and the basal ganglia appeared to be normal. The grey matter showed along with a reduced number of neurons a comparatively increased quantity of glial cells (Figure 4) most of which were found to be microglia, rather than astroglia or oligodendroglia, using appropriate stains (Figure 4 inset). The scarcity of neurons and the abundance of microglia were more evident in the parietal lobe of the right hemisphere but could also be seen throughout the grey matter of cerebral and cerebellar hemispheres of both sides. Cells with hypertrophic or *giant* character were not observed anywhere.

The histologic examination of lymphoid organs showed that the thymus had a normal structure and numerous well developed Hassal's corpuscles. The tonsils, Peyer's patches, lymph nodes and the appendix contained many lymphocytes but plasma cells, lymphoid follicles and germinal centers were rare (Figure 5). Many capillaries and venules with prominent endothelial cells were seen interspersed among the lymphocytes of every peripheral lymphoid tissue (Figure 6). The germinal centers of the spleen and most of the few observed in lymph nodes and tonsils had an *epithelioid* appearance showing a central core composed of large eosinophilic cells and lacking the usual dark outer cortex (Figures 7 and 8).

Final autopsy diagnosis: Asymmetric bilateral megalencephaly due to diffuse gliosis of malformative nature; hypertrophic lymphoid system with signals of exhaustion; left otitis media and meningitis.

## DISCUSSION

The most important points raised by this case concern the characterization of the asymmetrical enlargement of the brain and the hypothetical relationship between megalencephaly and lymphoid system deficiency.

In general, the distinction between unilateral and asymmetric bilateral megalencephaly is easily established since in the former there are usually homolateral hemigigantism, partial or global enlargement of half of the brain and absence of abnormalities of the other half (for a thorough review see Bignami et al.<sup>3</sup>). In some cases, however, this distinction is not so clear cut, namely because it is often very difficult to say whether or not the macroscopically uninvolved parts

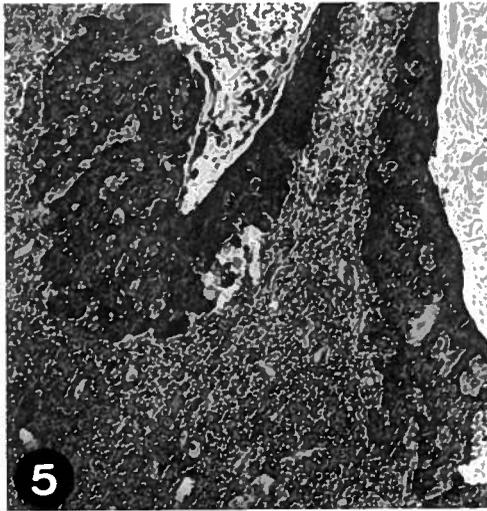


Figure 5: No follicles are seen in this tonsillar section. Hematoxylin-eosin, (X 40).

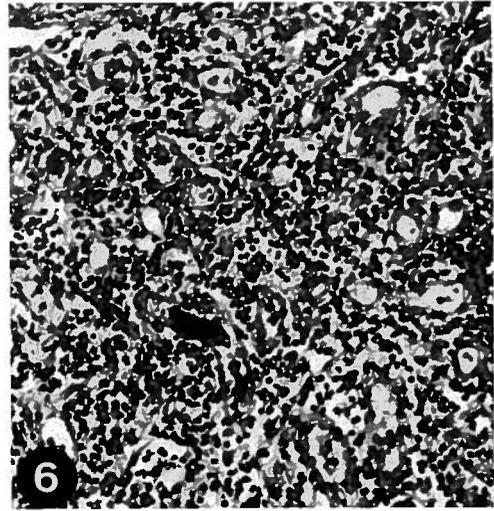


Figure 6: Many small vessels are seen among the lymphocytes of this lymph node. Hematoxylin eosin, (X 300).

of the brain are actually normal at the histological level. Bignami et al.<sup>3</sup> contributed to increase the confusion regarding such distinction, when they added some genetic considerations to the morphological evidence in order to classify as *unilateral* megalencephaly a case in which there was not homolateral hemigigantism and both halves of the brain appeared greater than normal.

Despite the macroscopical resemblance between our case and that of Bignami et al.<sup>3</sup> — both showed prominently enlarged parietal and temporal lobes of the right hemisphere — we see no reason to ignore the above-mentioned morphological criteria and therefore, we think that our case should be classified as asymmetrical bilateral megalencephaly rather than unilateral megalencephaly.

In many cases of megalencephaly there is a more or less evident family history.<sup>2</sup> In our case there was not. We did not also find, unlike Bignami et al.,<sup>3</sup> any karyotype abnormality, thus ruling out the interference of a mosaicism phenomenon.

Finally, the histologic appearance of our case does not match either that of Bignami et al.<sup>3</sup> since we have observed

a diffuse overgrowth of microglia throughout the grey matter without any apparent enlargement of neurons. This led us to the diagnosis of *asymmetric bilateral megalencephaly due to diffuse gliosis*<sup>4</sup> and raises some questions regarding the nature of such disorder.<sup>6</sup>

Overgrowth of glial cells — the so-called *diffuse gliosis* — can occur either as secondary reactive process in which astroglia usually plays a main role or as a primary proliferative process. In our case, the absence of another neurological disorder and the predominance of microglia does not support the reactive origin of the gliosis and points to its neoplastic or malformative nature.

It has been suggested that megalencephalies due to *diffuse gliosis* like that seen in the present case should be considered like tumors rather than malformations.<sup>6</sup> Although it is beyond the scope of this study to discuss such problem, we think that several facts support the malformative nature of our case. First, the diffuse increase of microglia did not interfere with the usual boundaries of grey and white matter, as one would expect in a neoplastic proliferation. Second, the coexistence of a striking asymmetric enlargement

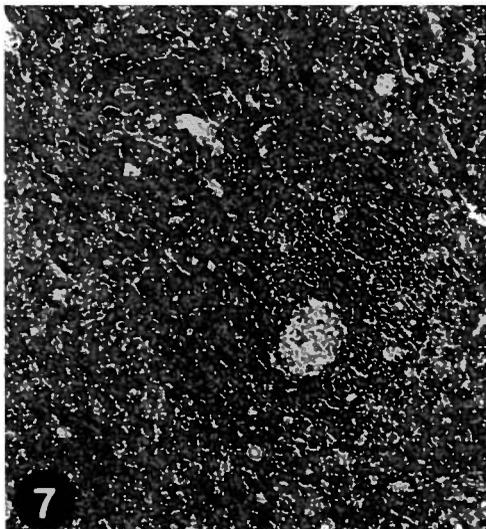


Figure 7: An epithelioid germinal center of the spleen. Hematoxylin-eosin, (X 40).

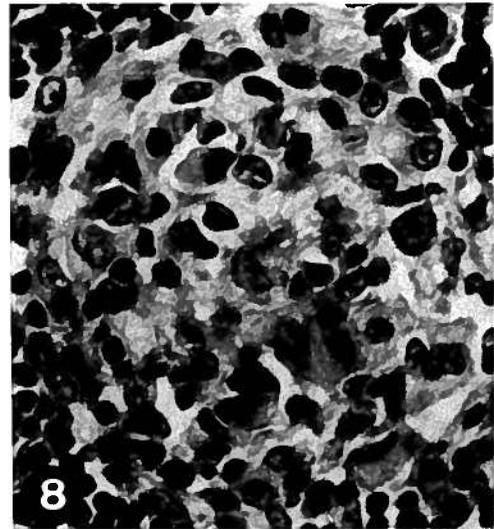


Figure 8: Epithelioid appearance of a spleen germinal center that lacks any dark outer cortex. Hematoxylin-eosin, (X 1,200).

of the right cerebral hemisphere with a diffuse overgrowth of glial cells throughout the grey matter does not fit the usual pattern of tumoral growth and finally the finding of micropolygyri over the more enlarged lobe points to a malformative abnormality rather than to a tumoral disorder.

Our finding of an hypotrophic lymphoid system might be thought to reinforce the advanced relationship between megalencephaly and lymphoid deficiency.<sup>4</sup> Such relationship has been based on the frequent association between megalencephaly and sudden death from infectious diseases, as well as on the finding of an underdeveloped lymphoid apparatus in two of the four cases, reported by Bartel.<sup>5</sup> Since the lymphoid system was not carefully studied in most of the cases of megalencephaly reported so far in the literature, we know neither the degree nor the type of the lymphoid abnormalities in such cases and, furthermore, we ignore if they have actually anything to do with the megalencephalic processes.

The scarcity of lymphoid follicles, germinal centers and plasma cells together with the peculiar epithelioid appearance of some germinal centers, support the assumption that a B lymphocyte deficiency could be present in our case.<sup>7</sup> However, we tend to consider these changes as the morphological expression of a cumulative effect of infection and bad nutrition rather than pointing to a primary defect of the immunologic system, and regard the epithelioid appearance of the germinal centers as the result of an overstimulation of the lymphoid system by the agents causing the otitis media and the meningitis. This view is supported by the absence of repeated infections in the previous history of the patient and by the preservation of a normal structure of every lymphoid organ.

In conclusion, we consider that there is enough morphologic evidence to rule out any major immunologic deficiency in the present case. This does not mean, however, that one can flatly exclude the possibility of some cases of megalencephaly being related to an immunologic deficiency, namely because of the large variety of neurologic conditions which are covered by the general descriptive term of megalencephaly.

## ACKNOWLEDGEMENTS

We are greatly indebted to Professors C. Nezelof and D. Serrão for their help in reviewing the case and to Mrs. M. Nascimento, M. L. Brito, M. G. Rodrigues and Mr. L. B. Nunes for their technical assistance. This study was granted by I.N.I.C. (projects MbP1 and MbP3).

## REFERENCES

1. NORMAN, R. M.: Megalencephaly. Greenfields Neuropathology. London, *Arnold*, 1963.
2. DeMYER, W. E.: Megalencephaly in children. *Neurology (Minneapolis)*, 1972; 22: 634.
3. BIGNAMI, A., PALLADINI, G., ZAPPELA, M.: Unilateral megalencephaly with nerve cell hypertrophy. An anatomical and quantitative histochemical study. *Brain Res*, 1968; 9: 103.
4. APLEY, J. SYMONS, M.: Megalencephaly: a report of 2 cases of hemihypertrophy. *Arch Dis Child*, 1947; 22: 172.
5. BARTEL, J.: Zur pathologischen anatomie des selbstmordes. *Wien Klin Wochens*, 1910; 23: 495.
6. FRIEDE, R. L.: Developmental Neuropathology. New York, *Springer*, 1975.
7. MILIKIN, P. D.: Epithelioid germinal centers. An acquired immunologic deficit? *Am J Clin Pathol*, 1977; 67: 545.

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