

MENTAL RETARDATION

A MRI study of 146 Brazilian children

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ABSTRACT - We report results of a magnetic resonance imaging (MRI) study of 146 Brazilian children, whose intelligence quotient scored less than 70. 50% of MRI examinations did not exhibit any signal of structural lesion (N group), whereas a focal thinning at the junction of the body and splenium of the corpus callosum; ventricular asymmetry; periventricular leukomalacia; gliosis and arachnoid cysts were among the most frequent findings in the remaining of subjects (L group). Maternal stress and altered blood pressure were the most frequent findings in the pre-natal history of both N and L children. Familial antecedents of mental deficiency were reported in 30% of both groups, whereas familiar history of alcoholism was important in N group (60% in N versus 0% in L groups). Neuropsychomotor development was delayed in 80% of the children in both groups. Aggressiveness is the most frequent finding in the post-natal children history.

KEY WORDS: mental retardation, magnetic resonance image, maternal stress, cerebral lesion, aggressiveness.

Deficiência mental: um estudo de ressonância magnética em 146 crianças brasileiras

RESUMO - Estudamos, através de ressonância magnética (RM), 146 crianças com quociente de inteligência menor que 70. 50% das RM não exibiram nenhum sinal de lesão (grupo N), enquanto adelgaçamento focal da junção do corpo e esplênio do corpo caloso, assimetria ventricular, leucomalácia periventricular, gliose e cisto aracnóide foram os achados mais freqüentes no restante das crianças (grupo L). Estresse materno e alteração da pressão arterial foram os achados mais freqüentes da história do pré-natal das crianças de ambos os grupos. Antecedentes familiares de deficiência mental apareceram em 30% de ambos os grupos. História de alcoolismo foi importante no grupo N. Atraso no desenvolvimento neuropsicomotor foi encontrado em 80% das crianças de ambos os grupos. Agressividade foi o achado mais freqüente na história pós-natal destas crianças.

PALAVRAS-CHAVE: deficiência mental, ressonância magnética, estresse materno, lesão cerebral, agressividade.

Mental retardation (MR) refers to organic brain dysfunction syndromes that are accompanied by significant cognitive limitation, reflected by an intelligence quotient (IQ) that is more than 2 standard deviations below the mean age on the test instrument used¹. Others, however, call it an administrative blanket term for a wide variety of different genetic, social and specific medical conditions sharing as common feature that affected individuals score below 70 on specific IQ tests². DSM-IV definition of mental defi-

ciency requires its onset to be established before age 18 years.

MR is frequently associated with other developmental disturbances, such as specific genetic syndromes, cerebral palsy, autism and communication disorders. It may be associated with psychiatric disorders or be the main manifestation of a brain malfunctioning¹⁻². Multiple etiological factors - including prenatal, perinatal and postnatal (not mutually exclusive) - are involved³. Therefore, the history of the preg-

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nancy, labor and delivery has to be investigated for clues of both intrinsic and extrinsic influences on the fetus and infant development¹. Intrauterine events may account for more than half of the causes of mental retardation, and they may be associated with maternal malnutrition, infection, alcoholism, health problems, etc¹⁻³. Perinatal factors may include placental insufficiency, complication of labor and delivery. However, perinatal events may be the consequence of previous intrauterine fetal problems rather than the primary cause of the brain malfunction resulting in mental retardation^{1,4}.

When not associated to syndromes - e.g. Down and Cerebral Palsy - MR is diagnosed in children referred due to motor or language developmental delays, or school difficulties¹⁻⁸. Is MR in these cases always associated with macroscopic brain lesions detectable by such techniques? And why such lesions did not result in any detectable signal or symptom? Or may it be the case that this type of MR results from cellular or synaptic abnormal development, undetectable by these techniques, without promoting any other visible neurological deficit?

Animal experiments have demonstrated that prenatal maternal stress affects pregnancy outcome and results in early programming of brain functions with permanent changes in neural-endocrine regulation and behavior in offspring⁴. Prenatal stress is associated with a range of adverse outcomes in humans, with evidences supporting the link between stress and the adverse birth outcomes of low birth weight and pre-term birth^{9,10}. There exists a trend for babies of high cortisol level mothers to be delivered earlier than those from the low cortisol group⁹. Increased maternal stress during pregnancy seems to be one of the determinants of temperamental variation and delay of development of infants and may be a risk factor for developing psychopathologies later in life^{10,11}.

The purpose of the present paper is to address the above questions through a magnetic resonance imaging (MRI) study of 146 children that scored less than 70 either on Stanford-Binnet Scale or Weschler Intelligence Scale, and whose main complaint were either motor and/or language development delays or school difficulties, and the analysis of their histories of the pregnancy, labor, delivery and postnatal life of the child.

METHOD

The present work studied 166 children aged from 7 to 19 years old, with IQ score less than 70 on the Stanford-Binnet Scale or Weschler Intelligence Scale for Children and

referred to a special institution for education of MR people, due to delayed motor and/or language development or learning difficulties. The presence (either confirmed or suspected) of any genetic syndrome was an exclusion criteria. Learning difficulty was characterized by the incapacity of the child to follow the regular program of the elementary school, as attested by the headmaster of the school where the child was enrolled.

The MRI studies were carried out in the Department of Radiology of the Clinics Hospital of the University of São Paulo in a 1.5 Tesla (Ge-Horizon) MR units. Children were not sedated for the MRI examination. Because of this 20 of these children were excluded because they did not cooperated with the MR examination. The following protocol was used: a conventional spin echo sagittal T1-weighted image (TR=510-640, TE=12-15 msec), conventional spin echo axial T1-weighted image (TR=500-640, TE=12-15 msec), fast spin echo axial and coronal T2-weighted acquisitions (TR=4400-4500, TE=100-120 msec, ET=8-16) and axial fluid attenuated inversion recovery-FLAIR (TR=8000, TE=150, TI=2300 msec). The slice thickness was 5-6 mm on axial images and 3 mm on coronal plane, the interslice gap varied from 0.3 to 0.6 mm. The field of view varied from 18-24 cm, the matrix ranged from 179-256 X 224-256, and NEX=2. The images on the coronal plane were orientated perpendicular to the hippocampus. To evaluate corpus callosum atrophy, the normal corpus callosum thickness was considered to be at the genu 1.1 ± 0.2 cm, at the body 0.6 ± 0.2 cm, and at the splenium 1.1 ± 0.2 cm¹². All MRI were classified by the same radiologist (C. C. Leite).

Data from the histories of the pregnancy, labor, delivery, pos-natal life and familial antecedents of the children were obtained by interviewing the child relatives or caretakers. These interviews were carried out by the physician and psychologist of the institution, using a standardized electronic protocol constructed by one (A. F. Rocha) of us.

The presence or absence of a clearly MRI identified brain lesion was used to classify children in two groups, namely, L - children with a clear brain lesion and N - children with no visible MRI lesion. The frequency of all findings related to the histories of the pregnancy, labor, delivery, pos-natal life and familial antecedents of the children were calculated for each group and compared by means of Yates corrected chi-squared. Since this is not intended to be a causal study we restricted the statistical analysis to univariate analysis, comparing both groups variable by variable without taking into account multiple comparisons for interactions between the variables. In a future work we intend to further the analysis of the present data set.

The study was approved by the ethical committees of the Hospital das Clínicas da FMUSP and APAE/Jundiaí.

RESULTS

Of the 166 children, 146 were submitted to the MRI study, aged 7 to 19 years (mean=15 years), of whom 88 (60.2%) were male and 58 (39.8%) were female. Their IQ varied from 45 to 70 (mean=64). 71 (48.6%) children presented normal (N group) exam-

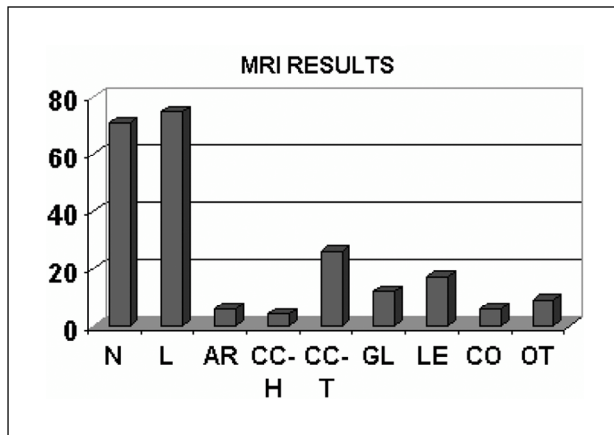


Fig 1. MRI findings. N, normal examinations; P, MRI with positive findings; AR, arachnoid cyst; ASV, ventricular asymmetry; CC-H, atrophy or dysgenesis of the corpus callosum; CC-T, thin corpus callosum isthmus; CO, colpocephaly; GL, gliosis; LE, periventricular leukomalacia; OT, other findings.

inations and 75 other (51.4%) presented pathologic (L group) MRI (Fig 1).

The most frequent MRI finding was a focal thinning at the isthmus of the corpus callosum (CC-T in Figs 1 and 2), in 26 (35.2%) of L group children. It was the only finding in 15 of these children (57%); in two of them it was associated with leukomalacia; in four others with ventricular asymmetry, and one had gliosis.

The second most frequent MRI finding was ventricular asymmetry in the axial and coronal plane (Figs 1 and 2). It occurred in 22 (29.4%) of the L group children: in 10 (45.4%) of the cases it was the only occurrence, and in two cases it was associated with leukomalacia.

The next most frequent MRI finding was leukomalacia associated or not with other lesions in the

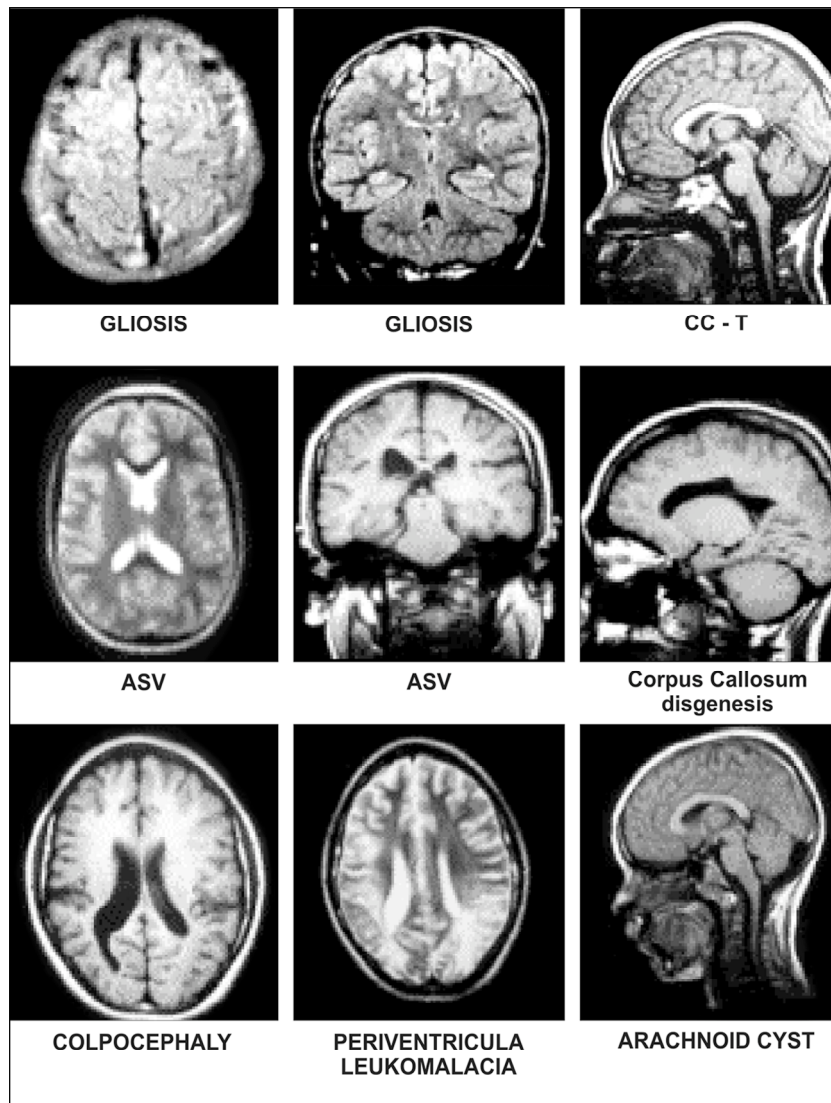


Fig 2. The most frequent MRI findings. See text for further details.

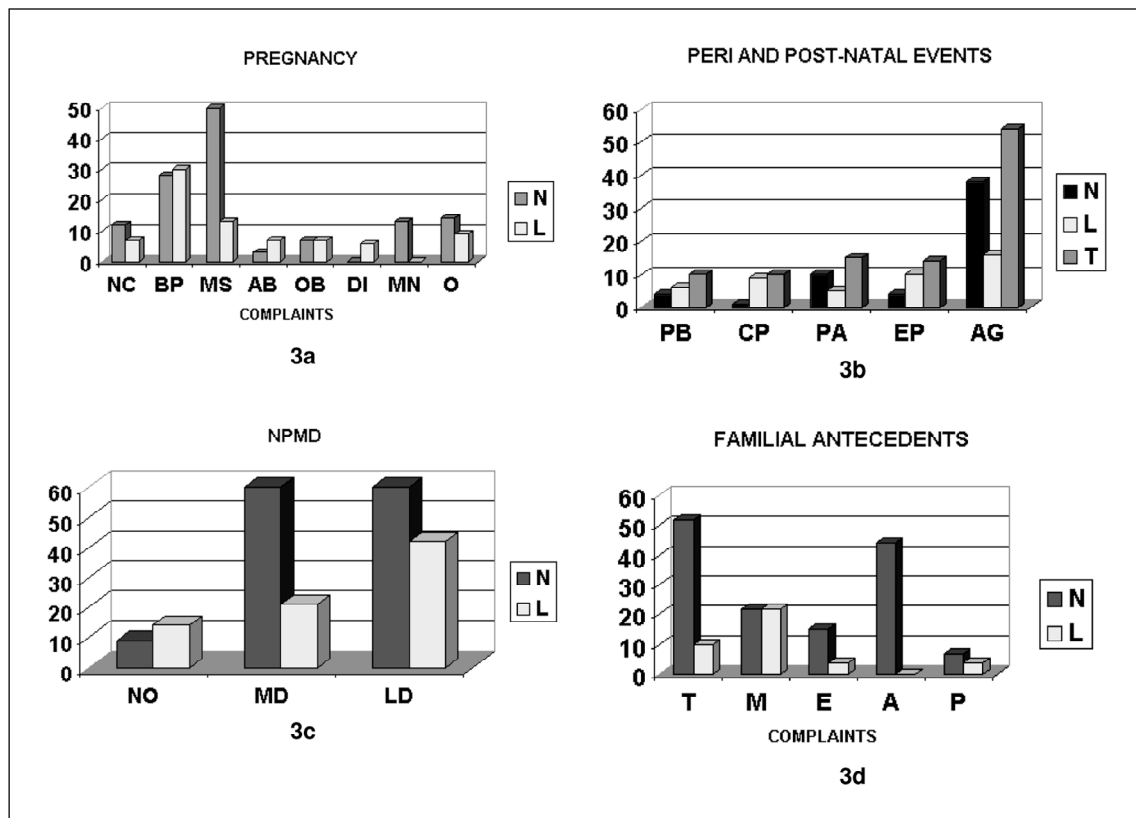


Fig 3. Historical data. N, normal MRI; L, lesion MRI. Pregnancy: NC, no complaint; BP, altered blood pressure; MS, maternal stress; AB, abortion attempt; OB, obstetric problems; DI, diabetes; MN, malnutrition; O, others. Peri and post-natal events: PB, premature birth; CP, cerebral palsy; PA, anxiety; EP, epilepsy; AG, aggressiveness. NPMD: NO, no developmental delay; MD, motor development delay; LD, language development delay. Familial antecedents: T, total; MD, mental deficiency; E, epilepsy; A, alcoholism; P, psychiatric disease.

periventricular region (Figs 1 and 2). These lesions presented hyperintensity on T2-weighted and FLAIR acquisitions. 17 children (22.6%) of the L group presented this finding, and in three cases it was associated with colpocephaly.

Another frequent finding identified in 12 (16%) of the L children was gliosis, defined as the presence of a round or oval white matter lesions that presented isointensity on T1-weighted images and hyperintensity on T2-weighted and FLAIR images.

Arachnoid cysts were found in 6 (9% of the L group) children. In three of the cases it was the only finding; in one case it was associated with corpus callosum dysgenesis, in another case with ventricular asymmetry and in the remaining case with unspecific white matter lesion. The global atrophy or hypogenesis of the corpus callosum occurred in 4 children (5%): in three cases it was associated with periventricular leukomalacia and in one child with arachnoid cyst.

Children of the N and L groups have different developmental histories as illustrated by Figure 3 and the statistical analysis is summarized in Table 1.

70% of mothers of N children and 17% of those from the L group ($p=0.00043$, $\chi^2=12.43$) reported emotional stress during pregnancy (N in Fig 3), related to domestic violence, economic distress, undesired pregnancy, and other familial problems. Spanking by husbands did not result in any reported relevant physical trauma to the mother or the fetus. High or low blood pressure (BP in Fig 3) was another common finding in both groups affecting around 40% of the mothers of both groups. Malnutrition (MN in Fig 3) affected 18% of mothers of the N group ($p=0.0003$, $\chi^2=12.90$), and according to them it was associated to the emotional stress. In contrast, no mother of the L group reported any nutrition problem. Abortion attempt (AB in Fig 3) attained a frequency of 4% in the N group and 9% in the L group ($p=0.024$, $\chi^2=5.15$). Bleeding, placental pathology and reduction of amniotic liquid - grouped here as obstetric interferences (OB) and labeled OB in Fig 3 - were reported by 9% of the mothers of both groups. Diabetes (DI in Fig 3) had a frequency of 14% in L and it was absent in N group ($p=0.0013$, Fisher exact test). Other

Table 1. Summary of the results.

	N	L	p	χ^2
MS	0.70	0.17	<0.00043	12.43
BP	0.39	0.40	0.92	0.01
MN	0.18	0.00	0.003	12.9
AB	0.04	0.09	0.02325	5.15
OB	0.10	0.09	0.86	0.03
DI	0.00	0.08	0.0013	Fischer
O	0.20	0.12	0.29	1.11
PB	0.06	0.08	0.29	1.11
CP	0.01	0.12	0.013	Fischer
PA	0.14	0.07	0.229	1.45
EP	0.06	0.13	0.19	1.68
AG	0.54	0.21	0.0001157	14.9
NO	0.13	0.19	0.14	2.14
MD	0.85	0.28	<0.00000001	35
LD	0.85	0.56	<0.00000001	26
M	0.31	0.29	0.07	3.24
A	0.62	0.00	<0.00000001	47.7
E	0.22	0.06	0.008	7
P	0.10	0.05	0.59	0.28

BP; altered blood pressure; MS, maternal stress; AB, abortion attempt; OB, obstetric problems; DI, diabetes; MN, malnutrition; O, others; PB, premature birth; CP, cerebral palsy; PA, anoxia; EP, epilepsy; AG, aggressiveness; NO, no developmental delay; MD, motor development delay; LD, language development delay; E, epilepsy; A, alcoholism; P, psychiatric disease.

claims (O in Fig 3) were associated with 14% and 19% of the L and N pregnancies ($p=0.29$, $\chi^2=1.11$). Only one mother of each group reported alcohol abuse during pregnancy.

Peri-natal anoxia (PA in Fig 3) was reported by 14% and 7% of the mothers from groups N and L ($p=0.229$, $\chi^2=1.45$). Premature birth (PB) occurred in 6% and 8% of births in groups N and L ($p=0.29$, $\chi^2=1.11$). Cerebral palsy (CP) was diagnosed in 1.4% and 12% of the children from groups N and L ($p=0.013$, Fisher exact test). Epilepsy (EP) was a manifestation in 6% of the children of the N group and in 13% of those in the L group ($p=0.19$, $\chi^2=1.68$). 53% of the children on the N group and 21% of those from the group L ($p=0.0001157$, $\chi^2=14.9$) were referred to the psychiatrist because of aggressive behavior (AG) at the school or home.

Motor development delay (MD in Fig 3) affected 85% of the N children and only 28% of those in L ($p<$

0.00000001 , $\chi^2=35$). Language (LD) development delay, however, affected 84% of the N children and 56% of those in L ($p<0.00000001$, $\chi^2=29$). 20% of the L and 12% of the N children did not experience any motor or language development delay ($p=0.14$, $\chi^2=2.14$).

The frequencies of the findings concerning familial antecedents were different in N and L ($p<0.00000001$, $\chi^2=43$). 75% of the children in the N group and only 25% in the L group are reported to have at least one relative with a history of alcoholism (A), epilepsy (E), mental retardation and psychiatric diseases (P). Alcoholism attained a frequency around 62% in N and was absent in the L group ($p<0.00000001$, $\chi^2=56$). Father alcoholism was a frequent finding. History of mental retardation in the family was present in 30% of each group. Epilepsy affected 22% of the relatives in the N group and 6% of those in L group ($p=0.008$, $\chi^2=7$). Psychiatric antecedents exhibited a frequency of 9% in the case of the N group and 6% in the case of L group ($p=0.28$, $\chi^2=3.24$).

DISCUSSION

Here we observed that MR is associated in 51.4% of the children (L group) with structural lesions identified by MRI such as, focal thinning of the corpus callosum at the isthmus level; asymmetry of the lateral ventricles; periventricular leukomalacia; atrophy or dysgenesis of the corpus callosum; congenital malformations; and round hyperintense lesions in the white matter identified on T2-weighted and FLAIR images.

Thompson et al.¹³ demonstrated an important growth at the callosal isthmus between ages 6 and 15 years, suggesting that cortico-cortical networks supporting rapid associative relay and language functions may myelinate more extensively and over longer periods than rostral fiber system. Castro-Caldas and Reis¹⁴ showed a reduction of the size of the areas near the callosal isthmus in illiterate people when compared to literate ones. McLeod et al.¹² hypothesized that the attenuations in the corpus callosum thickness may reflect areas where fusion was diminished, and there were less fibers crossing to the other cerebral hemisphere at that level. They found focal attenuations in the body of the corpus callosum in 35% of their patients, and considered this finding to represent a normal variant. Von Plessen et al.¹⁶ described a clear shape difference in the posterior mid-body of the corpus callosum between dyslexic and control subjects. Also, Krägeloh-Mann et al.¹⁷ found

a thinning of the corpus callosum in all children with mental retardation in their study. A focal thinning at the isthmus of the corpus callosum was found in 15 (10.3% of all MRIs) of our children, a fact that seems to confirm the pathological status of this anomaly of the corpus callosum. Also, global atrophy or hypogenesis of the corpus callosum occurred in 4 children and associated to leukomalacia in three of them. These four children experienced a very poor cognitive development.

Asymmetry of the lateral ventricles was the only MRI finding in 10 of these children (6.8% of all MRIs). In addition, motor development delay was associated with ASV in 60% of the cases and language development delay appeared in 70% of the ASV children. It seems therefore that asymmetry of the lateral ventricles is clearly associated with mental retardation in the present population. ASV has been associated with schizophrenia¹⁸, but it has been claimed to be a normal occurrence in the fetus and neonates¹⁹. Gilmore et al.²⁰ reported a mild enlargement of the lateral ventricles on prenatal ultrasound, which persisted in childhood and was associated with attention deficit hyperactivity disorder (ADHD), autism and learning disorders.

The periventricular leukomalacia refers to the lesions in the white matter dorsal and lateral to the external angle of the lateral ventricle, which are considered to be vascular borders zones at the premature infant²¹ characterized by focal necrosis, particularly at the level of the periventricular tissue at the level of the optic radiation adjacent to the trigone of the lateral ventricles and the frontal white matter adjacent to the Monro foramen²¹. Periventricular leukomalacia is manifested as hyperintense lesions on T2-weighted images, located in the peritrigonal regions with or without enlargement of the lateral ventricles. In some cases, the periventricular white matter in the frontal area is also affected¹⁷. Krägeloh-Mann et al.¹⁷ associated periventricular brain damage with mental retardation. Periventricular leukomalacia was identified in 17 of our 146 patients (11.7% of all MRIs).

Foci of hyperintense signal on T2-weighted and FLAIR images consist of small round or oval lesions located at the periventricular or subcortical white matter. In adults these lesions are common incidental findings on MRI images of the brain of control subjects or patients with a variety of diseases²². These lesions are believed to represent chronic low degree of vascular insufficiency with sub-clinical manifesta-

tion^{23,24}. This finding was identified in 12 of our patients (8.2% of the total population).

Maternal stress during the pregnancy was the most frequent finding reported by 63 mothers (43%) in the present study. Therefore, increased maternal stress during pregnancy seems to be an important risk factor for MR development in postnatal life. This is in accordance with the literature showing that maternal stress during pregnancy seems to be one of the determinants of delay developments of infants and may be a risk factor for development psychopathology later in life^{4,11,12,25}. Maternal stress was a complaint reported by 70% of mothers from the N group and by 17% of those from the L group ($p < 0.00043$). Therefore, it is a factor strongly associated with non-macroscopic brain insult, not detected by the MRI used here. Both animal and human studies have convincingly demonstrated that prenatal maternal stress affects pregnancy outcome and results in early programming of brain functions with permanent changes in neural-endocrine regulation and behavior in offspring^{4,10-12,25}.

The effect of maternal stress may be understood if it is accepted that the stress hormones from the mother induce an overproduction of fetal cortisol⁴. This augmented fetal cortisol in turn may damage the brain and/or increase the damaging effects of other factors such as deficient blood and nutrient supplies, or it may act as a cofactor increasing the pathological effects of factors involved with epilepsy and other mental or psychiatric malfunctions reported in the family²⁶⁻²⁹. The maternal stress effects are strongly influenced by hormones, and their outcomes are gender dependent²⁶. In agreement with this, it must be remarked that 88 (60.2%) of four children were male and 58 (39.8%) were female.

In the N group, maternal stress seemed to have magnified the effects of alcoholism, epilepsy, mental and psychiatric disturbs. It must be remarked that claims about these familial problems were low in the L group, and more than one type of claim were reported for more than one of the relatives in the N group. In particular, there is a high incidence (25%) of N alcoholic fathers and domestic violence was a major cause of maternal stress in this group. Indeed, Reichenheim, Moraes, and Hasselmann²⁹ reported that mothers from low income Brazilian families experienced domestic violence by partners involved with alcohol and drug abuse. Malnutrition affected 18% of mothers of the N group and it is probably another complicating factor. The composite effect of maternal stress, malnutrition and familial factors pro-

bably resulted in abnormal neurogenesis, explaining mental retardation and promoting motor and language developmental delays in 80% of the N children. Aggressiveness is also high among the children of the N group. Indeed, many authors^{10,11} have stressed that increased maternal stress during pregnancy seems to be one of the determinants of temperamental variation and delay of development of infants and may be a risk factor for developing psychopathology later in life. It is interesting to remark here that only three children of the N group were reported to be hyperactive.

Maternal stress in the L group was less important than in the case of the mothers of the N group. Abortion attempt and diabetes were also important occurrences in the L group. Perhaps maternal stress associated with blood pressure problems, abortion attempt, obstetric problems and diabetes could be facilitated the occurrence of the macroscopic lesions detected in the L group. High levels of stress hormones could have magnified fetal suffering due to reduced oxygen and nutrients supplies associated with maternal and placental hemodynamic disturbances. Such a composite effect might result into either gross lesions such as leukomalacia and ventricular asymmetry or more discrete and diffuse neural losses as in the cases of the gliosis and thinning of the corpus callosum at the isthmus level. Such lesions were associated to a motor development delay in 28% of the L children and language development delay in 56% of these subjects. This higher incidence of language compared to motor problems may be understood by the high frequency (17.8% of all MRIs) of corpus callosum isthmus anomaly. It must be remembered that Castro-Caldas and Reis¹⁴ showed a reduction of the size of the areas near the callosal isthmus in illiterate people when compared to literate ones. It is interesting to remark that perinatal anoxia was not a common event in the L group. Cerebral palsy occurred in 9 children of the L group and was predominant in this group in comparison with the N group. It seems that peri-natal anoxia was not the main determinant of both the lesions and cerebral palsy in the L group. Also, the present results did not point to a correlation between cerebral palsy and motor development delay.

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