CASE REPORT

FOCAL CEREBRAL INFARCTION IN NEWBORN: DESCRIPTION OF THREE CASES

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We observed 3 full-term newborns with focal ischemic injury of the middle cerebral artery (MCA), in which diagnosis of MCA stroke was suspected by US and confirmed by CT scan and MRI. A four-year follow-up was carried out to study the effect of neonatal stroke on neurodevelopmental outcome. All children had a history of pre-perinatal risk factors: neonatal cerebral infarction in term infants, in fact, has many possible causes, including bacterial meningitis, inherited or acquired coagulopathies, trauma and hypoxia-ischemia. The prognosis of neonatal MCA infarction depends on early diagnosis, on the CNS plasticity mechanism and, finally, on medical therapy and neuropsychological rehabilitation.

Infarction in the region of the middle cerebral artery can occur in both preterm as well as full term infants. Neonatal cerebral infarction in term infants has many possible causes, including bacterial meningitis, inherited or acquired coagulopathies, trauma and hypoxia-ischemia (1- 4).

Neonates with cerebral stroke do not present specific symptoms and the condition is usually insidious, so many atypical cases are not diagnosed properly during the neonatal stage. Neurological symptoms in the neonatal period are often subtle and non specific, even in infants with large infarctions involving an entire cerebral artery distribution. The most common presenting symptom is focal motor seizures of the controlateral limbs (5). Follow-up studies of known full term neonatal stroke indicate that most develop some form of hemiparesis, seizures disorder, cognitive difficulties or developmental delay during childhood (1).

Cranial magnetic resonance imaging is the most sensitive imaging modality to recognize infarction of a major artery in newborn infants. Some neonates with seizures and radiological evidence of an acute infarction can have congenital hemiparesis and/or emiplegia. Other patients have a normal neonatal course and present, in the following years, hemiparesis and imaging radiologic evidence of middle cerebral artery (MCA) stroke (6-8).

MATERIALS AND METHODS

We present 3 full-term newborns admitted to the Neonatal Intensive Care Unit of Chieti from January 1997 to March 2000 for neonatal seizures in which diagnosis of MCA stroke was suspected by US and confirmed by CT scan and MRI. These cases demonstrate that, even in full term neonates, born after normal

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pregnancy and delivery, with neonatal convulsion, the possibility of vasoocclusive brain infarction should be considered. The prognosis for neurological development appears to be variable: a four-year follow-up was carried out in all patients to study the effect of neonatal stroke on neurodevelopmental outcome (motor and cognitive functions, especially language acquisition and emotional and social development).

Patients
Case 1

C.A., a male infant, was the second child of a 27-year-old woman. Pregnancy was uncomplicated; at 39 weeks, a caesarean section was performed without difficulty, under general anesthesia. Birth weight was 4.0 kg. One and five-minute Apgar scores were both 9. On the first day of age, *clonic convulsion* to the right arm were noted. On admission the neurophysical examination was normal. During the hospital stay, the neonate showed tonic-clonic convulsions which were successfully treated with phenobarbital and clonazepam.

Laboratory investigations, coagulation values (prothrombin time, activated partial thromboplastin time, fibrinogen, antithrombin III, Protein C and S), TORCH and *fundus oculi* resulted normal. CFS values showed: positive Pandy reaction; 3 cells/mm³; protein 1.05; glucose 0.41. An intracranial ultrasound (US) examination revealed focal linear hyperechogenities localized at the level of the left Middle Cerebral Artery (MCA) branches, suggesting vascular perfusion ischemic abnormalities.

One week later, US findings were significantly abnormal with increasing echoes from infarcted areas. Sleep EEG recordings during the first week of life showed abnormal slow wave discharges over left fronto-central regions. CT scan showed a non-homogeneous hypodense area in temporo-parietal regions of the left hemisphere (Fig. 1).

One month later CT-scan showed a left front-temporal oval hypodense area with mass-effect determining a lateral ventricle compression with mieline shift. When the child was 2 months old, CT-scan and US showed a cerebral hemiatrophy with poroencephaly evolution. EEG was completely normal.

At the age of 12 months, MRI confirmed localization and topographic extension and evaluated the poroencephalic and multicystic evolution of the cerebral injury in the left MCA territory. Angio-MRI were normal.

Neurological examination showed a left convergent squint and a mild right upper extremity hemiparesis. The child was active and alert and seizure free. At 14 months, he could stand and crawl.

Case 2

B.C., a male newborn, was the first child of a 36-year-old woman. Pregnancy was normal. At 41 weeks gestation, there was spontaneous rupture of the membranes but with meconium stained fluid. Birth weight was 3.87 kg. The one- and five-minute Apgar scores were 8 and 10.

The infant, 36 hours after birth, was transferred to our Department because of the presence of seizures with left upper limb clonic movements, apnea, bradicardia, cyanosis, rapidly evolving into a *status epilepticus* with palpebral-oral movements and right inferior limb movements (such as pedalling, rolling). We treated with diazepam constant infusion until the seizures were controlled and with steroids for cerebral edema. Laboratory investigations were normal. Neurophysical examination was abnormal for the presence of increasing muscular tone of the inferior limbs, decreasing neck and upper limb muscular tone and left hemiparesis. US performed on the 2nd day of life showed right periventricular hyerechogenities. The following US recordings showed an increase of the previous findings and a right intra-parenchymal hyerechogenity over insula and centrum semiovalis for perfusional post-ischemic hemorrhage. EEG was performed after the first week of life and showed spikes in right and central regions with low high-voltage waves in the left frontal region; it was absolutely normal. CT, performed on the 4th day of life, confirmed the ischemic injury of the right MCA territory with a right lateral ventricle compression (for the presence of the cerebral edema); one month later CT showed a right hemiatrophy with a severe poroencephaly. Convulsions did not recur. At five months he showed a good ambiental sharing, a good head control but he presented mild left hemiparesis.

Case 3

M.C., a female newborn, was the first child of a 30-year-old woman. During pregnancy, she showed a fetal growth delay until 39 weeks, when, for a placenta detachment, it was necessary to do a caesarean section. Birth weight was 2.75 kg. One- and five-minute Apgar scores were 9 and 10, respectively. There were problems immediately after birth with upper and inferior limbs having repeated trembling.

Laboratory investigations, coagulation values and *fundus oculi* were normal. TORCH serologic test was negative. US, performed on the 1st day of life, showed a hypoechoic triangular image (a typical US ischemic outcome) in the left front-temporal region at the level of an MCA branch. Ten days later US findings were abnormal with increasing echoes from infarcted areas.

EEG recording was performed after the first week of life and showed high and medium voltage spikes in the right central region and high voltage low waves on the left frontal region. CT, performed on the 16th day after birth, showed an upper-cortical hypodensity in the left front-central region. Outcome EEG until the third month of life showed the previous bio-electric abnormalities. CT, at 40 days of age, confirmed the localization and the poroencephalic evolution of the cerebral injury; MRI showed a corpus callosum degeneration and a left frontal schizencephalic image (Fig. 3-4).

At 13 months of life, because the anterior fontanel was still open, the last US (Fig. 5) showed a characteristic hyperechoic "spider-like" image due to the glyosis and also showed a right hemiparesis.

We performed a four-year follow-up to study neuromotor, mental and linguistic evolution of all three patients, we analyzed them by, respectively, neurological examination, Stanford-Binner test of intelligence and Wescler Preschool and Primary Scales of Intelligence. They showed a normal mental evolution in cases 1 and 2, and a low-moderate mental retardation in case 3; moreover, neurological examination in case 1 showed only a left convergent squint, in case 2 a low left hemiparesis and, finally, a moderate right hemiparesis in case 3.

DISCUSSION

Cerebral infarction in the fetus and neonate is a more common occurrence than past estimates have suggested. The National Hospital Discharge Survey from 1980 to 1998 estimated that the perinatal stroke occurs in 1/4000 live births (9), but the incidence is probably underestimated because of variation in the presentation, evaluation and diagnosis. Most perinatal strokes are caused by thromboembolism from an intracranial or extracranial vessel, cardiac disorders, coagulation abnormalities and infection.

Pregnancy predisposes the mother and the fetus to relative hypercoagulability. Specific maternal diseases (including autoimmune disorders, pre-eclampsia and inherited thrombophilia) can expose the fetus to hypercoagulability and cerebral infarction. A late intrauterine placental thromboembolus predisposes cerebral infarction. In particular pre-eclampsia has been associated with coagulation defects that may contribute to
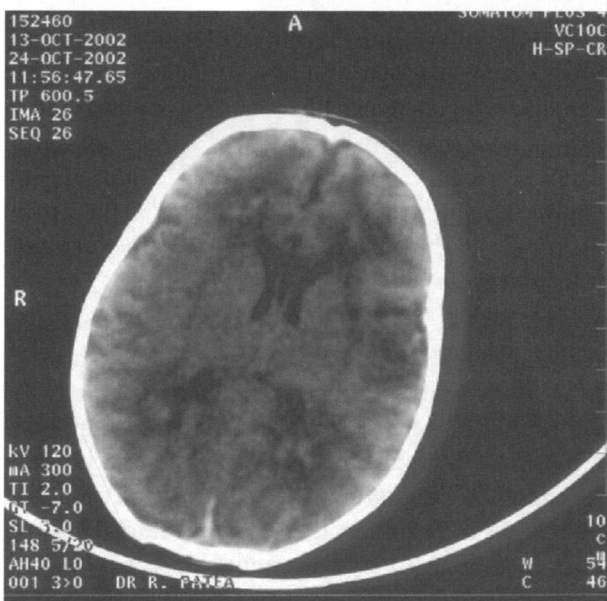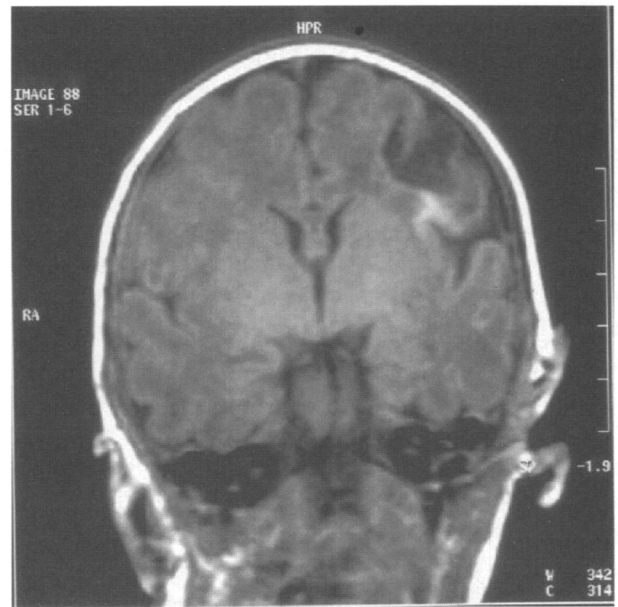

Fig.1.-*Case 1. CT scan: hypodense area in temporo-parietal regions of the left hemisphere.*
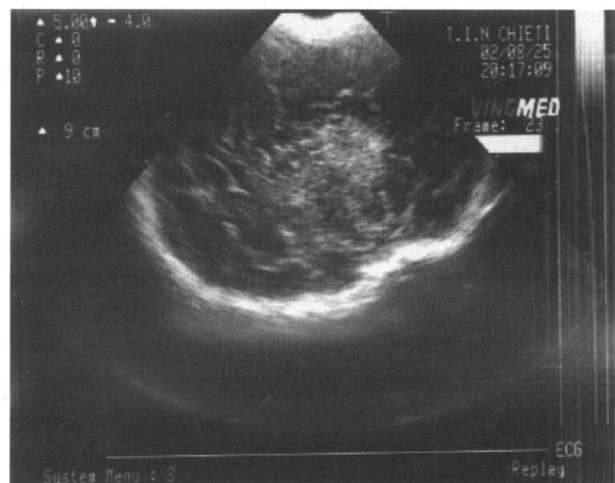
Fig.2.-*Case 2. Ultrasound findings: right periventricular hyperechogenities and ventricular asimmetry.*
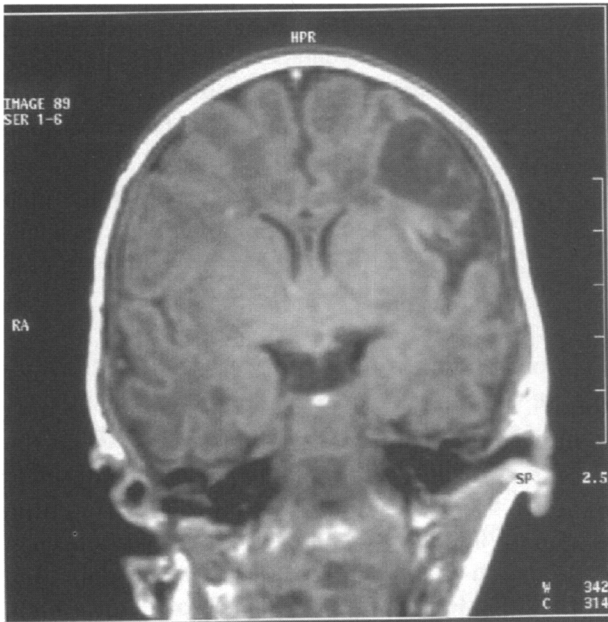
**Fig. 3.** *Case 3. MRI: Poroencephalic evolution in left frontal area.*

Fig. 4. *Case 3. MRI: Poroencephalic evolution in left frontal area.*

cerebral infarction in the newborn, carrying an increased risk of stroke in the mother and the fetus (10)

Abnormalities in the inhibitors for the activation of coagulation factors are associated with systemic and cerebral thrombosis in the neonatal period. Other risk factors in the newborn include disorders of spontaneous platelet aggregation, factor XII, prothrombin, heparin cofactor II and plasminogen. Occasionally, neonates with antithrombin III and protein C deficiencies have venous infarctions. Cerebral infarction may also be caused in the neonate during the birth process because of the aggravation of prothrombotic conditions by asphyxial stress (11).

Our findings confirm recent reports of cerebral infarcts in full-term infants born after normal deliveries and without predisposing factors, such as metabolic or infectious disturbances, polycytemia and congenital heart disease (2, 6, 8, 12). Moreover, our observations are in agreement with other authors (13-14) who demonstrated that children may survive and the clinical expression is variable (subtle seizures, focal or generalized convulsions, congenital hemiparesis).

Congenital hemiparesis is the most frequent consequence of perinatal occlusion of the middle
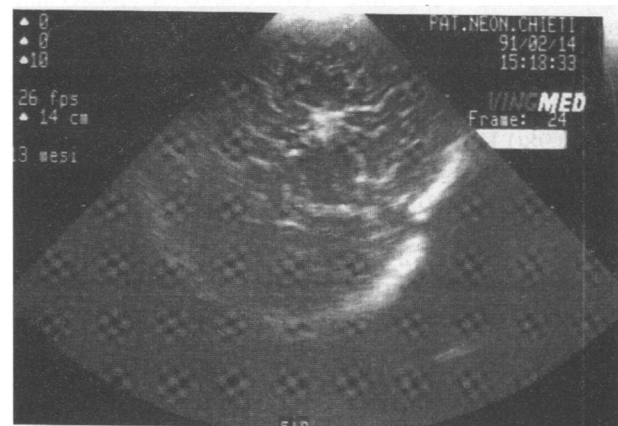
Fig.5.- *Case 3. Ultrasound findings: characteristic hyperechoic "spider-like" image due to the cicatritional gliosis.*

cerebral artery. Serial sonograms and CT scans of the infant's head, along with magnetic resonance angiography, are useful in making the diagnosis of cerebral infarction. With the advent of CT scanning, several studies (6, 8, 12) have been carried out to correlate the clinical manifestation of occlusion of MCA and the neurological evidence of cerebral damage. In fact neurophysiology and neuroimaging studies are complementary investigations for the detection of functional and structural deficits in the neonate associated with

cerebral infarction.

In 1980, a study (15) on 15 cases of occlusion of the middle cerebral artery showed that the vascular accident could have occurred in the uterus or during the perinatal period, following perinatal asphyxia, intrapartum trauma to cerebral vessels, umbilical venous catheterization, exchange transfusion, stretch injury of MCA in the absence of supratentorial subdural bleeding, supratentorial basal convexity, subdural haematoma and subsequent occlusion of MCA and arterial and venous thrombosis. No underlying aetiology can be found in many cases (2, 7, 12, 16-18).

In our patients, the diagnosis of vaso-occlusive disease was based on US scan and CT findings which were confirmed by MRI performed to exclude congenital vascular anomalies (17, 19).

CT scans demonstrated focal hypodensity areas within the first week of life in all our patients. This early sign would be one of the characteristics of neonatal cerebral infarction. On the other hand, persistent seizures after pre-perinatal stroke could also be related to these areas. US makes it possible to formulate the early suspicion of this pathology due to the presence of well defined triangular hyperechoic image and/or linear hyperechogenities in the basal ganglia arteries. Furthermore, US is a harmless, cheep neuroimaging technique and it is possible to perform it without moving the patient, so very easy to perform.

A prevalence of MCA in the left hemisphere observed by US and previously reported by Filipek in 76% of these patients, may be explained by the anatomy of the left carotid artery (20-22). On the contrary, Fujimoto did not emphasize the predominance of laterality (11). Bilateral infarction has been seen, in the early period of life, only in one of our cases and seems to be exceptional. We found hemorrhagic infarction in one of our three cases. We noted a mass effect in one case who had a normal neuropsychological development. These data indicate that mass effect could not be a sign of poor prognosis in neonates.

Clinical findings at onset and at follow-up are homogenous; this situation seems to be peculiar to the paediatric age and is different from what can be observed in adults. This difference can be due to the cerebral remodelling properties of the neonatal brain (23). Some studies have shown that the neonatal mammalian cerebral nervous system (CNS)

recovers from injury better than the adult one (11). This is probably related to two main anatomic reorganization processes:

1. new collateral fibers coming from the intact corticospinal pathways at a much great extent in neonates than adults;

2. less retrograde neuronal degeneration in neonates compared with that in adults (7). Moreover, the difference of long-term evolution of physical and neuromotor and linguistic development can be the result of anatomic injury in MCA distribution territory, which principally implicates the cortical motor areas of frontal lobe and fronto-temporal language areas, sparing the associative frontal and prefrontal areas.

In conclusion, there are a large number of perinatal, peripartum and postnatal risk factors that should be considered in the neonate with cerebral infarction. The evaluation should include serum studies to assess complete blood count, determination of glucose and serum electrolytes, disorders of metabolism and of coagulation (5). Reperfusion plays an important role in the pathophysiology of cerebral ischemia. Magnetic resonance imaging and histological studies in rat foca ischemia, usin transient middle cerebral artery occlusion, indicate that reperfusion after an ischemic episode of 2 or 3 hours duration does not result in reduction of the size of the infarct (24). Brief occlusion of the middle cerebral artery produces a characteristic, cell-type specific injury in the striatum, where medium-sized spinous projection neurons are selectively lost; this injury is accompanied by glyosis.

In the treatment of acute cerebral ischemic stroke, immediate re-canalization of the occluded artery, using systemic or local thrombolysis, is optimal for restoring the blood flow and rescuing the ischemic brain from complete infarction. However, the prognosis of neonatal MCA infarction depends on early diagnosis, on the CNS plasticity mechanism and finally on medical therapy and neuropsychological rehabilitation. In addition, in the presence of a newborn with seizures and/or emiplegia without metabolic, infectious and coagulation disturbances and congenital heart diseases, it is necessary to suspect a vascular pathology and use neuroimaging techniques (US, CT scan, MRI) to confirm the diagnosis and to

follow-up the evolution. Neonatal seizures history and the findings on neurologic examination at discharge help in counseling parents about the possible long-term outcome of neonatal stroke.

REFERENCES

1. **Lynch J.K. and K.B. Nelson.** 2001. Epidemiology of perinatal stroke. *Curr. Op. Pediatr. 13:499.*

2. **Chow G. and D. Mellor.** 2000. Neonatal cerebral ischaemia with elevated maternal anticardiolipin antibodies. *Dev. Med. Child Neurol. 42:412.*

3. **Carrilho I., E. Costa, M.S. Barreirinho, M. Santos, C. Barbot and J. Barbot.** 2001. Prothrombotic study in full term neonates with arterial stroke. *Haematologica 86:16.*

4. **Pignataro G., A. Tortiglione, A. Scorziello, L. Giaccio, A. Secondo, B. Seve, V. Santagata, G. Caliendo, S. Amoroso, G. Di Rienzo and L. Annunziato.** 2004. Evidence for a protective role played by Na(+)/Ca(2+) exchanger in cerebral ischemia induced by middle cerebral artery occlusion in male rats. *Neuropharmacology 46:439.*

5. **Miller V.** 2000. Neonatal cerebral infarction. *Semin. Pediatr. Neurol. 7:278.*

6. **Molteni B., G. Oleari and E. Fedrezzi.** 1990. Relation between CT patterns clinical findings and etiological factors in children born at term affected by congenital hemiparesis. *Neuropediatrics 18:75.*

7. **Roodhoot A.M., P.M. Parizel, K.J. Van Acker, A.J.R. Depreneze and P.J. Van Reempts.** 1994. Idiopathic cerebral infarction with paucity of symptoms in the full-term neonates. *Pediatrics 80:381.*

8. **Volpe J.J.** 2001. Neurology of the Newborn. W.B. Saunders Company. Philadelphia, p. 415.

9. **Lynch J.K., D.G. Hirtz and G. De Veber.** 2002. Report of the National Institute of Neurological Disorders and Stroke: workshop on perinatal and childhood stroke. *Pediatrics 109:116*

10. **Ott W.J.** 2003. Middle cerebral artery blood flow in the fetus and central nervous system complications in the neonate. *J. Maternal Fetal Neonatal. Med. 14:26.*

11. **Scher M.S., M. Wiznitzer and B.A. Bangert.** 2002. Cerebral infarctions in the fetus and neonate: maternal-placental- fetal considerations. *Clin. Perinatol. 29:693.*

12. **Fujimoto S., K. Yokochi, H. Togary, Y. Nishimura, K. Inumai and M. Futamura.** 1992. Neonatal cerebral infarction: symptoms, CT findings and prognosis. *Brain Develop. 14:48.*

13. **Mercuri E., S. Anker, A. Guzzetta, A. Barnett, L. Haataja, M. Rutherford, F. Cowan, L. Dubowitz, O. Braddick and J. Atkinson.** 2003. Neonatal cerebral infarction and visual function at school age. *Arch. Dis. Child Fetal Neonatal. Ed. 88:487.*

14. **Mercuri E., A. Barnett, M. Rutherford, A. Guzzetta, L. Haataja, G. Cioni, F. Cowan and L. Dubowitz.** 2004. Neonatal cerebral infarction and neuromotor outcome at school age. *Pediatrics 113:95.*

15. **Kulakowski S. and J.C. Larroche.** 1980. Cranial computerized tomography in cerebral palsy. An attempt at anatomoclinical and radiological correlation. *Neuropediatrics 11:339.*

16. **Richard K.S., S.N. Mc Gregor, J.F. Pasternack and S.E. Neely.** 1995. Fetal stroke associated with elevated maternal anticariolipin antibodies. *Obstet. Gynecol. 80:3.*

17. **Govaert P., P. Vanhaesebrouck and C. De Praeter.** 1994. Traumatic neonatal intracranial bleeding and stroke. *Arch. Dis. Child. 67:840.*

18. **Temesvari P.** 2000. Perinatal cortical infarction with no obvious cause. *Arch. Dis. Child Fetal Neonatal. Ed. 83:77.*

19. **D'Orey M.C., M.J. Melo, I. Ramos, H. Guimaraes and N.T. Santos.** 1999. Cerebral ischemic infarction in newborn infants. Diagnosis using pulsed and color Doppler imaging. *Arch. Pediatr. 6:457.*

20. **Lovblad K.O., K. Ruoss, R. Guzman, G. Schroth and C. Fusch.** 2001. Diffusion-weighted MRI of middle cerebral artery stroke in a newborn. *Pediatr. Radiol. 31:374.*

21. **Filipek P.A., K.S. Krishnamoorthy, K.R. Davis and K. Kuehnie.** 1987. Focal cerebral infarction in newborn: a distinct entity. *Pediatr. Neurol. 3:141.*

22. **Bories J., S. Derhy and J. Chiras.** 1985. CT in hemispheric ischemic attacks. *Neuroradiology 27:468.*

23. **Chugani H.T., D.A. Shewmon, W.J. Peacock, W.D. Shiels, J.C. Mazziotta and M.E. Phelps.** 1988. Surgical treatment of intractable neonatal-onset seizures, the role of Positron Emission Tomography. *Neurology 38:1178.*

24. **Nagashiro S., M. Uno, K. Sato, M. Morioka and Y. Ushio.** 1998. Pathophysiology and treatment of cerebral ischemia. *J. Med. Invest. 45:57.*