

SELECTIVE INJURY OF THE GLOBUS PALLIDUS IN CHILDREN WITH POST-CARDIAC SURGERY CHOREIC SYNDROME

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Choreoathetosis has been recognized as a complication of cardiac surgery requiring deep hypothermia and extracorporeal bypass since a report of brain damage in 10 children treated with these techniques (Björk and Hultquist 1960). Choreoathetosis was subsequently reported as a particular problem after cardiac surgery for congenital heart defects in both cyanotic and acyanotic infants and children (Bergouignan *et al.* 1961, Delay *et al.* 1961, Drew 1961, Brunberg *et al.* 1974). Since the early 1960s, deep hypothermic cardiac arrest (DHCA) has become a central feature of cardiac surgery in young patients. It now permits the cardiac surgeon to carry out definitive corrective surgery on patients with congenital heart disease during the first few weeks of life, with good results in the great majority (Venugopal *et al.* 1973, Subramanian 1983). Improved techniques (especially hemodilution during bypass) and improved filters have greatly reduced the risk of adverse neurological events, but postoperative chorea remains a significant problem, with a reported incidence of around 1 or 2 per cent since 1980 (Clarkson *et al.* 1980, Chaves and Scaltsas-Persson 1988, Robinson *et al.* 1988, DeLeon *et al.* 1990, Kececioglu *et al.* 1990, Wical and Tomasi 1990, Wong *et al.* 1992).

The neuropathology of this complication

has been elusive. In the reports cited above, the picture was complicated by more widespread neurological and neuropathological changes secondary to emboli and overt ischemic damage with death in the early postoperative period. More recent reports with pathological studies have been scarce and incomplete (Chaves and Scaltsas-Persson 1988, Robinson *et al.* 1988). We report the clinical and neuropathological findings in two patients with cyanotic congenital heart disease who developed the typical choreoathetosis syndrome in relative isolation from other neurological symptoms and signs. One infant survived for two weeks after surgery, and the other survived for four weeks, allowing assessment of the neuropathology in the early phase of their illness.

Subjects and method

Clinical records of both infants were reviewed. Both patients had also been examined during life by one of the authors (C.F.B.). Complete postmortem examinations were performed according to standard protocols. The brains were immersion-fixed in buffered 20 per cent formalin for two weeks, then sectioned and examined macroscopically. Sections for microscopic examination were embedded in paraffin wax and stained with hematoxylin and eosin/Luxol fast blue,



Fig. 1. Case 1: lateral globus pallidus. Loss of nerve cells and myelin staining with fragmentation of myelin sheaths (arrows). Luxol fast blue/cresyl violet $\times 800$.

cresyl violet/Luxol fast blue, Bodian silver method, phosphotungstic acid/hematoxylin, gallocyanin, and Lapham's method for myelin. Immunohistochemical staining was performed on selected sections with alkaline phosphatase/fast red chromogen using antibody to glial fibrillary acidic protein (GFAP) (Dako).

Case summaries

CASE 1

This 27-month-old girl had been born after an uncomplicated term pregnancy and delivery. Her birthweight was 2800g. At 17 days of age she developed respiratory distress and was found to have Wolff-Parkinson-White syndrome due to congenital heart disease with atrial septal defect, multiple ventricular septal defects, stenosis of the aortic isthmus and a hypoplastic unilobar right lung (scimitar syndrome). The arrhythmia responded to digoxin, propranolol and frusemide, but she remained dusky at rest, and became mildly cyanotic when crying. Her later development was normal, and on admission at age two to Boston Children's Hospital for surgical correction she was

beginning to count and to learn the alphabet.

She underwent hypothermic cardiac bypass surgery with patch closure of the atrial septal defect, incorporation of the anomalous right pulmonary vein through a pericardial baffle into the left atrium, and ligation of three large aortopulmonary collateral vessels. An endocardial incision was made near the tricuspid valve, but the bundle of His was not obliterated. Cardiopulmonary bypass time was 104 minutes, with 44 minutes of circulatory arrest. During the operation, esophageal and tympanic temperatures were recorded at 12°C, and the hematocrit was maintained at 18 to 19 per cent. The intra-operative and immediate postoperative course were complicated by severe supraventricular tachycardia (SVT) with hypotension. She was weaned from the ventilator on the second postoperative day, and discharged from the intensive-care unit in mild respiratory distress on postoperative day four. Episodes of SVT were managed with cardiac pacing, digoxin and procainamide.

On the fourth day, episodes of



Fig. 2. Case 1: medial globus pallidus. Preservation of nerve cells, but loss of myelin staining and fragmentation of myelin sheaths. Luxol fast blue/cresyl violet $\times 800$.

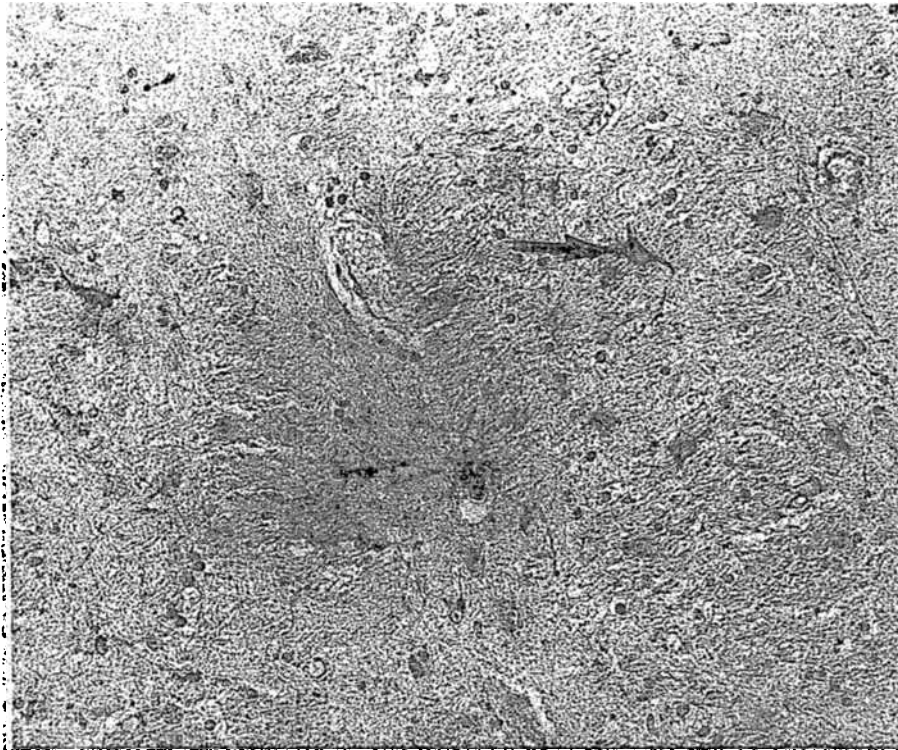


Fig. 3. Case 1: lateral globus pallidus. Scattered hypertrophic astrocytes (arrows) with visible cytoplasm and cytoplasmic processes. GFAP immunocytochemistry $\times 660$.

hypertension of the trunk were noted. During the subsequent two weeks she continued to have respiratory distress, cardiac arrhythmia and fever. It was noted that she was 'in constant motion' when awake, and 'restless and flailing' during episodes of SVT. Because of continuing respiratory distress and right-to-left shunt, she underwent closure of the ventriculoseptal defect with 75 minutes cardiac arrest time. Postoperatively she became increasingly agitated, with non-purposeful choreic and ballistic movements that increased on stimulation and decreased with sleep or heavy sedation with diazepam and morphine. She was hypotonic with normal reflexes and bilateral plantar flexor responses. CT scan showed 'diffuse loss of brain mass' without a focal lesion. She continued to decline, and died following an episode of bradycardia one month after the first operation.

Neuropathological examination

Gross examination of the brain showed mild enlargement of the lateral and third ventricles, but normal brain weight. On microscopic examination, the cerebral neocortex appeared well preserved and the white matter was appropriately myelinated. There were rare microscopic foci of neuronal loss, with mild rarefaction of neuropil and reactive astrogliosis in the CA1 region of the hippocampus. The putamen and caudate nucleus appeared well preserved. Rare calcospherites were seen and some glial nuclei were vesicular.

There was marked neuronal loss in the globus pallidus (Fig. 1; and comparison case, Fig. 5), greater in the lateral than in the medial segment. Myelin staining was pale in the globus pallidus, and fragments of myelin were present in both lateral (Fig. 1) and medial (Fig. 2) segments. Macrophages were sparse, but hypertrophic astrocytes and glial fibers could be seen with immunohistochemical staining for GFAP (Fig. 3). The lenticular fasciculi, pallidothalamic fasciculi and subthalamic nucleus appeared vacuolated and myelin fragments could also be seen in pallido-subthalamic fiber bundles traversing the internal capsule.

With GFAP immunostaining, reactive

astrocytes were seen in small numbers in the neostriatum, including the nucleus accumbens, the medial thalamus and the hypothalamus, and were interdigitated among the fibers of the lenticular fasciculus and posterior limb of the internal capsule. Brainstem, cerebellum and spinal cord were well preserved except for the cerebellar dentate nucleus, which contained scattered acutely necrotic neurons with hypereosinophilic cytoplasm and pyknotic nuclei.

CASE 2

This 2½-year-old boy was born after an uncomplicated term pregnancy and delivery weighing 2700g. Cyanosis and heart murmur noted at nine weeks of age led to a diagnosis of tetralogy of Fallot with pulmonary atresia and multiple systemic-to-pulmonary collateral vessels. He was admitted to hospital because of pneumonia at six and 19 months of age. He walked alone at 18 months, and by the time of admission to the Children's Hospital at 2½ years he was speaking in three- to five-word phrases with a vocabulary of approximately 100 words.

Following repeat cardiac catheterization, hypothermic cardiopulmonary bypass surgery was performed, with placement of an aortic homograft between the right ventricular outflow tract and the hypoplastic left and right pulmonary artery junction site. Cardiac bypass time was 112 minutes, with 29 minutes of circulatory arrest. Intraoperative esophageal and tympanic temperatures were 12 and 15°C, respectively, and the hematocrit was maintained at 22 to 26 per cent. Postoperatively he was lethargic but arousable, with normal movement of the extremities.

Sedation was instituted on postoperative day two, to control 'thrashing' movements. Four days postoperatively he developed abnormal jaw movements and tongue thrusting, followed by increasing ballistic and choreiform movements of the extremities, which were fully evolved by postoperative day six. He was hypotonic, with reduced reflexes but normal plantar responses, and developed episodes of conjugate upward deviations of the eyes lasting approximately 30 seconds. CT scan showed a parietal lesion

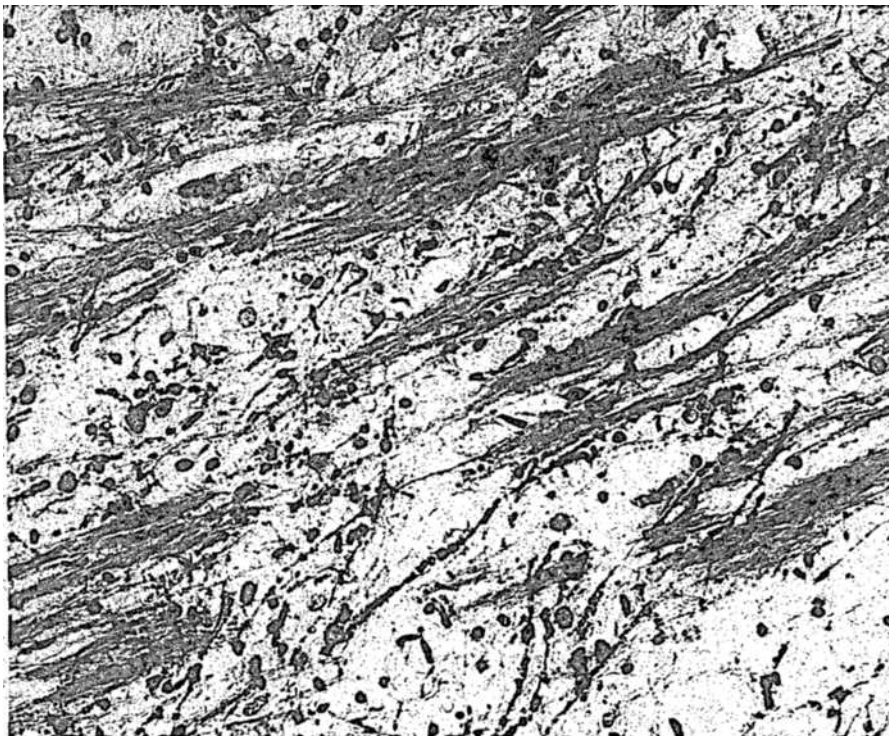


Fig. 4. Case 2: lateral globus pallidus. Loss of nerve cells and myelin fragmentation similar to that seen in case 1. Luxol fast blue/cresyl violet $\times 800$.

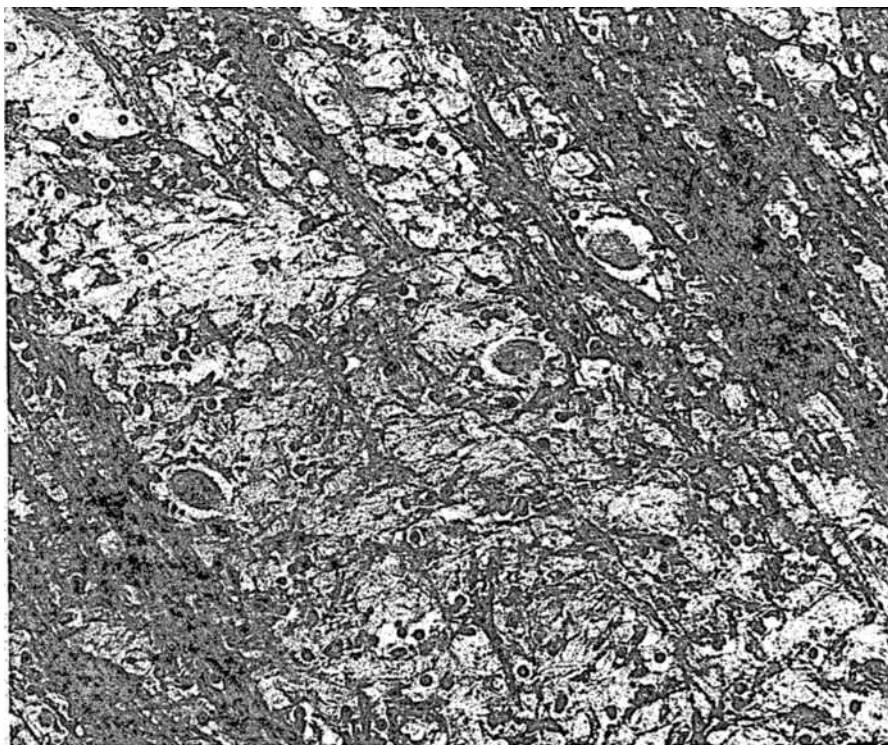


Fig. 5. Comparison case (34-month-old boy with gastro-intestinal lymphangiectasia and no history of neurological disease): lateral globus pallidus with normal density of nerve cells and myelin staining. Luxol fast blue/cresyl violet $\times 800$.

consistent with old infarct. The abnormal movements persisted except during sleep, despite therapy with carbamazepine, haloperidol and chlorazepam. They were diminished by deep sedation with lorazepam and chloral hydrate. Atrial dysrhythmias developed 15 days post-operatively, and on the next day—following an episode of vomiting and cyanosis—he developed cardiorespiratory arrest and died.

Neuropathological examination

Grossly, the brain was normal in weight. On microscopic examination, there was a small cavitated old infarct in the left inferior parietal lobule, which involved the cortex and subcortical arcuate fibers, but did not extend into the deeper parietal white matter. Wallerian degeneration was found in the white matter underlying the infarct. No evidence of thrombus or embolus was identified. The caudate nucleus, putamen, subthalamic nucleus, thalamus and hippocampus appeared well preserved, except for the presence of a small number of scattered calcospherites in the neostriatum.

There was neuronal loss in the globus pallidus, chiefly in the lateral segment (Fig. 4; and comparison case, Fig. 5). Myelin staining was also diffusely decreased (though less markedly than in the previous case), and myelin fragments were present. Reactive astrocytes were less prominent than in case 1. With GFAP immunostaining, small numbers of reactive astrocytes were seen in the centrum semiovale and the corpus callosum on the side of the infarct, and also focally in the dorsomedial nucleus of the thalamus and the medial hypothalamus. A few vacuoles and axonal spheroids were seen in the central tegmental tract of the pons. The brainstem, cerebellum and spinal cord otherwise appeared well preserved.

Discussion

The most prominent neuropathological abnormality in these two young patients with choreoathetosis subsequent to cardiac surgery with DHCA involved the external globus pallidus and consisted primarily of loss of neurons, nerve fiber degeneration and gliosis. The localization

was consistent with current concepts of clinical correlation (Mitchell *et al.* 1989), but the pathological changes were subtle and did not indicate the pathogenesis of the lesion. The lack of frank necrosis and vascular change argues against the concept of microcirculatory 'no-reflow', embolic infarction and severe generalized anoxic-ischemic injury. The localization implies a special vulnerability of the globus pallidus to some aspect of the operation. Ferry's (1990) review of neurological complications from a survey of six cardiac surgery centers also suggested that there was a management variable, in that only three of the six centers reported postoperative chorea.

Though the first report of chorea following cardiopulmonary bypass and DHCA appeared in 1960, and noted the presence of injury to the globus pallidus, the pathological findings also included widespread abnormalities reflecting overt ischemia or regional circulatory failure (Björk and Hultquist 1960). Few subsequent early reports included neuropathological findings. The employment of hemodilution during bypass, improved filters and other technical advances have greatly reduced embolic and overt ischemic brain damage and lowered the earlier prohibitive mortality rate from DHCA (Mayer 1991). Nevertheless, since 1988 six publications (Robinson *et al.* 1988, DeLeon *et al.* 1990, Kececioglu *et al.* 1990, Wical and Tomasi 1990, Wong *et al.* 1992, Huntley *et al.* 1993) and two abstracts (Chaves and Scaltsas-Persson 1988, Medlock *et al.* 1992) have indicated that the complication of this movement disorder has persisted. However, these reports have given details of only two cases with pathology studies. Among the five children with choreic syndrome reported by Robinson *et al.* (1988), no brain abnormalities 'in addition to those of Down's syndrome' were seen in one autopsied child with Down syndrome and tetralogy of Fallot who died five months postoperatively and had recovered from a choreic syndrome approximately one month before death. One autopsied case from the four children reported by Chaves and Scaltsas-Persson (1988) showed 'hypoxic neuronal degeneration and capillary proliferation in the basal

ganglia', but further details are not available.

The postoperative chorea syndrome seen in these children appears to be primarily a complication of cardiopulmonary bypass with hypothermia, with the added risk factor of induced cardiac arrest in the majority of patients. The central feature of the clinical syndrome is a movement disorder consisting of chorea or ballismus, oculomotor abnormality and hypotonia, characteristically arising after an asymptomatic latent period of one to seven days. Most of the severely affected patients who survive have also had significant mild-to-moderate cognitive abnormalities.

Among all the similar clinicopathological disorders that may provide some insight into the problem, perhaps the closest is the choreoathetosis reported by Perlman and Volpe (1989) in preterm infants with bronchopulmonary dysplasia. An identical movement disorder appeared at about three months of age. These seriously ill infants required continuous treatment using a ventilator and oxygen. Neuropathology study was available for one infant, who showed a 'moderate degree of neuronal loss with astrocytosis in caudate, putamen, globus pallidus and thalamus'. The authors hypothesized that chronic hypoxia was a likely cause, as in these infants the deficient oxygenation was not acute but chronic.

The mechanism for the pallidal damage in the setting of DHCA remains uncertain. Neuropathology studies in both adults and children treated with cardiopulmonary bypass have demonstrated a variety of brain lesions, including thrombo-embolic infarctions, diffuse or segmental necrosis in the cerebral cortex (especially calcarine cortex), hippocampus and medial globus pallidus, and focal or diffuse white matter necrosis, especially in young infants (Aguilar *et al.* 1971, Terplan 1976, Bozóky *et al.* 1984). Lack of tissue necrosis in the pallidum and relative sparing of other brain regions such as the hippocampus, usually regarded as highly susceptible to hypoxic-ischemic damage, suggest either that hypothermia significantly ameliorates the tissue reaction to such damage or that a mechanism other than hypoxia-ischemia is responsible.

The clinical data indicate that the age of the patient is an important factor. The literature and our own experience indicate that infants tend not to be vulnerable during the first four to six weeks of life, and that up to 10 or 12 months chorea is likely to be mild and usually reversible. The syndrome primarily affects older infants and children to mid-childhood, and has seldom been reported in adults (Egerton *et al.* 1963). In this context, the finding of Chugani *et al.* (1987) that the metabolic rate for glucose in humans between three and nine years was significantly higher than values in infants and adults in all regions of the brain including the lenticular nucleus may be important. Positron emission tomography, however, did not permit separate analysis of the globus pallidus. Also of possible relevance is the interesting observation that there is transient glutaminergic innervation in the rat globus pallidus in early life that is several times greater than values at birth or in the adult, with a peak on the seventh postnatal day (Greenmyre *et al.* 1987). The data suggest that there are high values in two- and six-week-old infants, but no developmental time course was reported.

The consistent risk factors during surgery are hypothermia and cardiopulmonary bypass. In the majority of the reported patients, and in almost all of those admitted to the Boston Children's Hospital (Wong *et al.* 1992), another factor has been the total circulatory arrest that is carried out to obtain a bloodless field during a critical phase of the operation. These risk factors are all consistent with the hypothesis that the injury to the globus pallidus is anoxic-ischemic in origin, and that complete tissue necrosis is prevented by hypothermia. Nevertheless, it is clear that additional factors are required because the complication only occurs in one or two per cent of patients, and duration of bypass, duration of cardiac arrest and depth of hypothermia have not proved to distinguish between affected and unaffected patients.

The anecdotal report of Drew (1961), that slowing the rate of cooling made a significant difference in incidence, has not been confirmed or denied by systematic

study. However, it is clear in our own studies of 13 patients at Boston Children's Hospital with severe choreoathetosis that some developed the disorder even though the duration of cooling time was extended to up to an hour (Wong *et al.* 1992). We also found marginally significant differences in the cooling time to cardiac arrest, and slightly more significant variation in cooling and warming rates, as well as in depth of cooling between patients with and without chorea. While the hypothesis that 'cold shock' is solely responsible has not stood the test of time, rapid cooling has nevertheless been shown experimentally to lead to very uneven rates of cooling in the body and brain of dogs (Almond *et al.* 1964). A role for alterations in regional cerebral blood flow was suggested by Aoyagi *et al.* (1975), who noted a significant reduction in blood flow to the globus pallidus during re-warming after hypothermia in infant baboons. Greeley *et al.* (1989) measured cerebral blood flow with xenon clearance techniques in infants and children undergoing deep hypothermic cardiopulmonary bypass (with or without total circulatory arrest) and found decreased cerebral blood flow because of temperature reduction with loss of cerebral pressure-flow autoregulation. They also noted impairment of cerebral reperfusion in the patients who had also been subjected to total circulatory arrest with 'alpha-stat' management (see below).

Perhaps more significant are the pre-operative reduction of pulmonary collateral vessels, which may steal blood from the brain especially during the

cooling and re-warming period (Wong *et al.* 1992), and the management of CO₂ and pH during the bypass ('alpha stat' vs 'pH stat') (Wong *et al.* 1992, Jonas *et al.* 1993). The change from 'pH stat' management (in which CO₂ is added to the perfusion mixture) to 'alpha stat' (in which it is not) has been associated with a noticeable increase in postoperative chorea and a worsened developmental outcome in infants (Wong *et al.* 1992). The increased level of CO₂ of the pH stat management presumably increases cerebral blood flow during bypass and could be a significant factor in the pathogenesis of brain damage.

Neither the pathology nor the clinical data currently provide an answer to this problem, which probably centers around the several factors that may lead to partial ischemia. There will have to be further studies of these factors and of the vulnerability of the pallidum in the setting of hypothermic cardiopulmonary bypass.

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SUMMARY

Occasionally children undergoing cardiac surgery using cardiopulmonary bypass with deep hypothermia and cardiac arrest develop a postoperative syndrome of acute chorea. The authors report the neuropathological findings in two such children surgically treated for congenital heart disease. Examination of the brain showed neuronal loss, reactive astrocytosis and degeneration of myelinated fibers (without frank necrosis) in the globus pallidus, primarily the outer segment, with sparing of other regions commonly susceptible to hypoxic-ischemic necrosis. The localization and relative mildness of the brain damage suggest a susceptibility of the globus pallidus to injury in this setting and implicate disruption of pallidal pathways in the pathogenesis of post-cardiac surgery choreic syndrome.

RÉSUMÉ

Atteinte sélective du noyau lenticulaire chez l'enfant, dans les syndromes choréïques suivant une chirurgie cardiaque

Il arrive que des enfants subissant une chirurgie cardiaque pour shunt cardiopulmonaire, et présentant une hypothermie profonde et un arrêt cardiaque, présentent un syndrome choréïque aigu post-opératoire. Les auteurs rapportent les données neuropathologiques chez deux enfants traités pour malformation cardiaque congénitale. L'examen du cerveau révéla une perte neuronique, une

réaction astrocytaire et une dégénérescence des fibres myélinisées (sans nécrose franche) dans le noyau lenticulaire, principalement la partie externe, les autres régions pouvant communément souffrir d'une nécrose hypoxique-ischémique étant épargnées. La localisation et la relative modération du dommage cérébral suggèrent une susceptibilité du noyau lenticulaire aux lésions et une interruption des voies lenticulaires dans la pathogénie du syndrome choréique survenant après une chirurgie cardiaque.

ZUSAMMENFASSUNG

Selektive Globus pallidus Verletzung bei Kindern mit Chorea Syndrom nach Herzoperation
Nach einer Herzoperation mit Herz-Lungenmaschine, Hypothermie und Herzstillstand entwickeln Kinder gelegentlich postoperativ ein akutes Chorea Syndrom. Die Autoren berichten über die neuropathologischen Befunde bei zwei solcher Kinder, die wegen eines kongenitalen Herzfehlers operiert worden waren. Die Untersuchung des Gehirns ergab Verlust von Neuronen, reaktive Astrozytose und Degeneration der myelinisierten Fasern (ohne freie Nekrose) im Globus pallidus, hauptsächlich im äußeren Segment, wobei die anderen Regionen, die gewöhnlich für hypoxisch-ischämische Nekrosen anfällig sind, ausgespart blieben. Die Lokalisation und die relative Geringfügigkeit des Hirnschadens lassen eine Anfälligkeit des Globus pallidus für Schädigungen dieser Art vermuten und haben eine Unterbrechung der Bahnen des Pallidums als Ursache des Chorea Syndroms nach Herzoperation zur Folge.

RESUMEN

Lesión selectiva del globus pálido en niños con síndrome coreico post cirugía cardíaca
Ocasionalmente niños a los que se les ha practicado una cirugía cardíaca utilizando un by-pass cardiopulmonar con hipotermia profunda y paro cardíaco sufren un síndrome postoperatorio de corea aguda. Los autores aportan los hallazgos neuropatológicos en dos casos así tratados por padecer una enfermedad cardíaca congénita. El examen del cerebro mostró pérdida neuronal, astrocitosis reactiva, y degeneración de fibras mielinizadas (sin franca necrosis en el globus pálido) sobre todo del segmento externo, con indemnidad de otras regiones comunmente susceptibles a la necrosis hipóxica-isquémica. La localización y relativa poca importancia de la lesión cerebral sugiere una susceptibilidad del globus pálido a la lesión e implica una disrupción de las vías palidales en la patogenia del síndrome coreico post cirugía cardíaca.

References

- Aguilar, M. J., Gerbode, F., Hill, J. D. (1971) 'Neuropathologic complications of cardiac surgery.' *Journal of Thoracic and Cardiovascular Surgery*, **61**, 676-685.
- Almond, C. H., Jones, J. C., Snyder, H. M., Grant, S. M., Meyer, B. W. (1964) 'Cooling gradients and brain damage with deep hypothermia.' *Journal of Thoracic and Cardiovascular Surgery*, **48**, 890-897.
- Aoyagi, M., Flasterstein, A. H., Barnette, J., von Koch, L., Ross, J. N., Kennedy, J. H. (1975) 'Cerebral effects of profound hypothermia (18°C) and circulatory arrest.' *Circulation*, **51**(52 (Suppl. 1)), 52-59.
- Bergouignan, M., Fontan, F., Trarieux, M., Julien, J. (1961) 'Syndromes choréiformes de l'enfant au décours d'interventions cardio-chirurgicales sous hypothermie profonde.' *Revue Neurologique*, **105**, 48-56.
- Björk, V. O., Hultquist, G. (1960) 'Brain damage in children after deep hypothermia for open-heart surgery.' *Thorax*, **15**, 284-291.
- Bozóky, B., Bara, D., Kertész, E. (1984) 'Autopsy study of cerebral complications of congenital heart disease and cardiac surgery.' *Journal of Neurology*, **231**, 153-161.
- Brunberg, J. A., Doty, D. B., Reilly, E. L. (1974) 'Choreoathetosis in infants following cardiac surgery with deep hypothermia and circulatory arrest.' *Journal of Pediatrics*, **84**, 232-235.
- Chaves, E., Scalfas-Persson, I. (1988) 'Severe choreoathetosis following congenital heart disease surgery.' *Neurology*, **38** (Suppl. 1), 284. (Abstract.)
- Chugani, H. T., Phelps, M. E., Mazziota, J. C. (1987) 'Positron emission tomography study of human brain functional development.' *Annals of Neurology*, **22**, 487-497.
- Clarkson, P. M., McArthur, B. A., Barrat-Jones, B. G. (1980) 'Developmental progress after cardiac surgery using hypothermia and cardiac arrest.' *Circulation*, **62**, 855-861.
- Delay, J., Deniker, P., Ginestet, D., Verdeaux, G., Verdeaux, J., Rausch de Traubenberg, N. (1961) 'Effets neuro-psychiques des interventions avec arrêt circulatoire prolongé en hypothermie profonde.' *La Presse Médicale*, **69**, 2539-2542.
- DeLeon, S., Ilbawi, M., Arcilla, R., Cutilletta, A., Egel, R., Wong, A., Quinones, J., Husayni, T., Obeid, M., Sulayman, R. (1990) 'Choreoathetosis after deep hypothermia without circulatory arrest.' *Annals of Thoracic Surgery*, **50**, 714-719.
- Drew, C. E. (1961) 'Profound hypothermia in cardiac surgery.' *British Medical Bulletin*, **17**, 37-42.
- Egerton, N., Egerton, W. S., Kay, J. H. (1963) 'Neurologic changes following profound hypothermia.' *Annals of Surgery*, **157**, 366-374.
- Ferry, P. (1990) 'Neurologic sequelae of open-heart surgery in children: an irritating question.' *American Journal of Diseases of Children*, **144**, 364-373.
- Greeley, W. J., Ungerleider, R. M., Smith, L. R., Reves, J. G. (1989) 'The effects of deep hypothermic cardiopulmonary bypass and total circulatory arrest on cerebral blood flow in infants and children.' *Journal of Thoracic and Cardiovascular Surgery*, **97**, 737-745.
- Greenmyre, T., Penny, J. B., Young, A. B., Hudson, C., Silverstein, F. S., Johnston, M. V. (1987) 'Evidence for transient perinatal glutaminergic innervation of globus pallidus.' *Journal of Neuroscience*, **7**, 1022-1030.
- Huntley, D. T., Al-Mateen, M., Menkes, J. H. (1993) 'Unusual dyskinesia complicating cardiopulmonary bypass surgery.' *Developmental Medicine and Child Neurology*, **35**, 631-641.
- Jonas, R. A., Bellinger, D. C., Rappaport, L. A., Wernovsky, G., Kickey, P. R., Farrell, D. M., Newburger, J. W. (1993) 'Relation of pH strategy and developmental outcome after hypothermic

- circulatory arrest.' *Journal of Thoracic and Cardiovascular Surgery*, **106**, 362-368.
- Kececioğlu, D., Hanefield, F., Becker, E. (1990) 'Akute Chorea nach Herzoperation in Hypothermie und totalem Bypass.' *Klinische Pädiatrie*, **202**, 115-116.
- Mayer, J. E. Jr. (1991) 'Development, growth, and cardiac surgery.' *American Journal of Diseases of Children*, **145**, 33-34.
- Medlock, M. D., Cruse, R. S., Geiss, D. M., Winek, S. J., Aldag, J. C. (1992) 'A 10-year experience with post-pump chorea including evaluation with positron emission tomography.' *Annals of Neurology*, **32**, 443. (Abstract.)
- Mitchell, I. J., Jackson, A., Sambrook, M. A., Crossman, A. R. (1989) 'The role of the subthalamic nucleus in experimental chorea.' *Brain*, **112**, 1533-1548.
- Perlman, J. M., Volpe, J. J. (1989) 'Movement disorder of premature infants with severe bronchopulmonary dysplasia: a new syndrome.' *Pediatrics*, **84**, 215-218.
- Robinson, R., Samuels, M., Pohl, K. (1988) 'Choreic syndrome after cardiac surgery.' *Archives of Disease in Childhood*, **63**, 1466-1469.
- Subramanian, S. (1983) 'Management of cardiopulmonary bypass in infants and children: deep hypothermia and circulatory arrest.' In Glenn, W. W., Baue, A. E. (Eds.) *Thoracic and Cardiovascular Surgery*. Norwalk, CT: Appleton Century Crofts, pp. 644-654.
- Terplan, K. L. (1976) 'Brain changes in newborns, infants, and children with congenital heart disease in association with cardiac surgery. Additional observations.' *Journal of Neurology*, **212**, 225-236.
- Venugopal, P., Olszowka, J., Wagner, H., Vlad, P., Lamberg, E., Subramanian, S. (1973) 'Early correction of congenital heart disease with surface-induced deep hypothermia and circulatory arrest.' *Journal of Thoracic and Cardiovascular Surgery*, **66**, 375-386.
- Wical, B. S., Tomasi, L. G. (1990) 'A distinctive neurologic syndrome after induced profound hypothermia.' *Pediatric Neurology*, **6**, 202-205.
- Wong, P. C., Barlow, C. F., Hickey, P. R., Jonas, R. A., Castaneda, A. R., Farrell, D. M., Lock, J. E., Wessel, D. L. (1992) 'Factors associated with choreoathetosis following cardiopulmonary bypass in children with heart disease.' *Circulation*, **86** (Suppl. 2), 118-126.