LETTERS TO THE EDITOR

Serum S-100 protein levels after pediatric cardiac surgery: A possible new marker for postperfusion cerebral injury

To the Editor:

We read with great interest the publication of Lindberg and associates¹ in this Journal on the serum S-100 protein levels after pediatric cardiac surgery.

In our institution we have used this marker as a routine biochemical monitoring parameter before and after corrective cardiac operations in infants. We have published several studies concerning the release patterns of S-100 in association with other neurologic monitoring methods, such as near-infrared spectroscopy and transcranial Doppler sonography.

We have also found a close relationship between the age and weight at operation and the measured peak values before and after cardiopulmonary bypass (CPB).² Our postoperative release patterns in infants and children are similar to those results of Lindberg and colleagues. The postoperative peak values correlated to age ($r = -0.77$, $P < .0001$) and weight ($r = -0.71$, $P < .0001$) of the studied infants.²

In the study of Lindberg and associates, however, we miss the presence of a control group to show that the protein S-100 levels are not similarly increased after operations without CPB. As appropriate controls, we use infants undergoing corrective surgery for coarctation of the aorta without CPB.

It remains unclear whether these transient elevations of postbypass S-100 values indicate "normal patterns," inasmuch

as infants with evident clinical brain injury had much higher levels, more than 2 SD of those without cerebral and neurologic complications (Fig 1). Possible subclinical brain injury associated with transient elevation of the serum levels of protein S-100, therefore, have to be evaluated with the use of additional neurophysiologic methods and neurodevelopmental follow-up studies. Higher serum concentrations than the peak S-100 values in all infants were found in 5 infants with neurologic and cardiac complications (Fig 1).

Seizure activity during the early postoperative period has been suggested to have powerful neurologic predictive value in follow-up of infants after corrective surgery in early life.⁴ This is in agreement with our findings and with the observation of Lindberg in one case in his study, in which a marked increase of the protein S-100 serum levels was found immediately after the onset of seizure activity.¹

We also agree with Lindberg and his coauthors' speculation that the possible lack of maturation of the blood-brain barrier may be a factor causing the higher release of protein S-100 in neonates than in infants.² However, in addition to the inflammatory processes, oxygen-derived free radicals induce endothelial reperfusion injury and may contribute to the alteration of the blood-brain barrier.⁵ Thus measurement of malondialdehyde, a fragment of lipid peroxidation, in the serum may provide possible information on accentuated structural membrane injury⁵ by free radicals.^{5,6}

Significant increases of malondialdehyde values, as well as

Fig 1. Release patterns of S-100 protein in infants and children with and without neurologic abnormalities. CT, Computed tomography; TOF, tetralogy of Fallot; IVH, intraventricular hemorrhage; d-TGA, dextro-transposition of the great arteries; CAVC, complete atrioventricular canal; CPB, cardiopulmonary bypass; SD, standard deviation.

a concomitant significant increase of the serum concentration of the astroglial protein S-100, were found between cross-clamping and unclamping of the aorta.⁶

In conclusion, we found similar age-dependent release patterns of the protein S-100 in neonates and infants in comparison with infants undergoing surgery without CPB. A pathologic mechanism underlying the release of protein S-100 in the serum might be an induced reperfusion injury and possible transient functional and/or structural alteration of the brain-blood barrier.

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Reply to the Editor:

We thank Abdul-Khaliq and his associates for their interest and for their informative response to our article, published in the August 1998 issue of the Journal (*J Thorac Cardiovasc Surg* 1998;116:281-5). We were primarily interested in evaluating the occurrence of S-100 in serum in pediatric patients of different ages undergoing operations with extracorporeal circulation (ECC). Retrospectively, it would have been interesting to have S-100 levels also in pediatric patients having undergone other kinds of operations without ECC. However, Abdul-Khaliq and associates have finished studies including

infants undergoing surgery without ECC. Ideally these studies will show how surgery without ECC will affect the pattern of S-100 protein release to serum in pediatric patients.

Our intention was to correlate elevations in S-100 with neurologic injuries. We perform approximately 270 to 320 pediatric cardiac operations with ECC yearly, including repairs of arterial switch, truncus arteriosus, and total anomalous pulmonary venous drainage and Norwood I-III stage operations; however, during our study period, and to date, we have had only 1 child with clinical neurologic symptoms. The figure of the S-100 protein pattern in 5 infants with neurologic complications, included in the letter by Abdul-Khaliq and associates, shows increased levels (>12.5 g/L) 24 hours after the operation. This confirms the finding of a delayed increase in S-100 protein in serum in children with neurologic complications and is an important complement to our findings.

Children arrive at the hospital 2 days at most before the operation. This short time schedule often inhibits preoperative neuropsychometric assessment, which is of utmost importance if postoperative neurologic dysfunction is to be ascribed to perioperative events. Sophisticated neuropsychometric tests are not applicable during the first week after the operation, when ventilatory treatment, sedation, and opiates frequently are being used. We routinely send the children back to their home hospitals throughout Sweden as soon as possible if no complications appear. Inasmuch as most of the children still need some form of pain relievers, neuropsychometric and neurophysiologic tests may be irrelevant during this period after an operation. These factors were taken into consideration before the study started, and we decided to rely on clinical neurologic signs that demonstrated significant cerebral consequences, observed in the intensive care unit or in the cardiology ward before the patients were dismissed to their home hospitals.

In conclusion, there are obviously many questions still to be answered regarding the mechanisms of the postoperative release of the S-100 protein in children. We are awaiting the results of the studies on the subject by Abdul-Khaliq and his associates.

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Invited letter concerning surgical repair of recurrent aortic coarctation

To the Editor:

Sakopoulos and colleagues¹ have provided a very useful service to physicians caring for children and adults with coarctation of the aorta by reviewing a recent series of patients with recurrent aortic coarctation who were managed surgically. Their results demonstrate that improvements in surgical technique and modern preoperative, intraoperative,