Postnatal decrease in substantia nigra echogenicity
Implications for the pathogenesis of Parkinson’s disease

Introduction

Recent studies have revealed that patients with idiopathic Parkinson’s disease (PD) show an abnormal signal shift of substantia nigra (SN) echogenicity on transcranial sonography (TCS) [2, 7, 14]. Ninety percent of all PD patients have a distinct increase in SN signal brightness (echogenicity) on TCS, suggesting that it may be an interesting paraclinical sign for PD. While SN hyperechogenicity is typical for PD it is also found in about 9% of healthy subjects [3]. Several lines of evidence point towards a subclinical alteration of the nigrostriatal system in some of the healthy subjects with SN hyperechogenicity [1]. Therefore, it has been suggested that this ultrasound sign may serve as a vulnerability marker for nigral injury.

The reason underlying increased signal intensity of the SN in PD patients remains unclear, yet. Two consecutive studies indicated that SN hyperechogenicity is related to an increase of tissue iron content associated with higher L- and H-Ferritin levels [6, Zecca et al., unpublished]. Noteworthy, SN echogenicity is inversely related to the neuromelanine content (Zecca et al., unpublished). Considering the close link of neuromelanine and dopaminergic cell count, it is therefore assumed that subjects exhibiting elevated SN echogenicity may have lower dopaminergic cell numbers at the SN.

However, if iron is one factor provoking the increase in SN echogenicity one may ask at which stage of brain maturation iron starts to accumulate. Therefore, we set out to examine newborns and children by TCS to determine the echo pattern of the SN at this age period to get
more insight into the normal iron metabolism of this area.

**Patients and methods**

109 newborns, infants and children aged 0 to 192 months were included into this study after informing their parents, that the routinely performed rating of the SN would be used to find normal values of SN echogenicity in children (median age 6 [2, 132 months], 65 boys and 44 girls). Thirteen of these children were prematurely born and examined before the 40th week of pregnancy. Fifty children were aged 0≤1 2 months, four 1≤5 years, seven 5≤10 years, thirty 10≤15 years, and five sixteen years. Children were examined at the Department of Child Neurology and Neurosurgery, St. Petersburg and at the Department of Child Neurology and Neonatology of the University in Tübingen using an ALOKA 1100 (Japan) and an Acuson XP 128 ultrasound system equipped with a 3 and 5 MHz sector transducer. The thirteen children examined on the ward in Tuebingen were prematurely born and had the examination as part of a general ultrasound screening for newborns. Reasons for consulting the outpatients care in St. Petersburg were also routine examinations. Inclusion criteria were the absence of any neurological symptoms and any data on organic damages of the brain and the existence of an adequate temporal bone window to conduct TCS through the intact skull.

Transcranial sonographic examination was performed following the protocol described previously [2, 11]. The brain was scanned through the temporal bone windows. At first, the investigator identified the butterfly-shaped brainstem. Thereafter, the examiner attempted to visualize hyperechogenic signals superimposing the SN as clearly as possible. Echogenicity (signal brightness) is not quantifiable using ultrasound. In the past, this limitation has been avoided either by semi-quantitative assessment using a scoring system or by planimetric measurements of the extent of hyperechogenic signal at the SN. Both procedures correspond sufficiently with the visual impression and have been shown to be adequately reproducible [3, 7, 8]. Here we used the scoring system graduating signal intensity on a three point scale: no or minimal echogenic signal at the SN (comparable with signal extension below 0.05 cm²), score 0, only mild echogenic signal at the SN (comparable signal extension 0.05–0.12 cm²) score 1, moderate hyperechogenic SN (signal extension 0.13–0.19 cm²) score 2, distinct hyperechogenic SN (signal extension above 0.19 cm²) score 3 (see also Figure). After rating SN echogenicity on one side ultrasound examination was performed through the contralateral temporal acoustic bone window to determine echogenicity scores of the opposite SN. To ensure equal performance of the scanning and rating procedure, the ultrasound scans of both centers were sent to the same specialist, who evaluated them for the correct scanning plane and judged the grading. In none of the cases there was a disagreement about the grade chosen by the first investigator.

**Results**

The median echogenicity score was 1.6 (0; 3) (median value, 25th and 75th percentile) for the right side and 1.8 (1; 3) for the left side. Distribution of echogenicity scores are outlined in the Table. We found a clear relation of echogenicity scores and age of the children with newborns having higher echogenicity scores than older children (Pearson correlation: r: –0.739, –0.616; p < 0.001 for the right and left SN, Figure). While 77 % (48 of 63) of infants in their first year of life had a distinct echogenic SN at least on one side (score 3), this echogenicity score was detected in only 17 % (6/35) of children older than 10 years, a number getting close to the ratios found in adults. On the other hand 2 of 63 infants in their first year had no or only minimal echogenic signals at one or both SNs (score 0) while this echo feature was seen in 21