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Original article

Serum tau protein level serves as a predictive factor for neurological prognosis in neonatal asphyxia

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Abstract

Background: Tau protein is a microtubule-associated protein that is present in axons. Elevated tau protein levels in cerebrospinal fluid or serum are associated with several central nervous system diseases and can indicate neuronal injury. *Objective:* In the present study, we measured and then compared serum tau protein levels between infants with neonatal asphyxia and control subjects. We examined these data to investigate the correlation between serum tau protein levels and neurological outcomes after neonatal asphyxia. *Patients and methods:* Serum tau protein levels were determined by an enzyme-linked immunosorbent assay in 19 neonates with neonatal asphyxia. Of these 19 neonates, 3 had severe spastic tetraplegia, and 1 had west syndrome. A group of 19 unaffected neonates was included in the study as a control group. *Results:* Serum tau protein levels on postnatal day 3 were significantly higher in the poor outcome group than those in the good outcome ($p = 0.010$) and control groups ($p = 0.006$). On postnatal day 7, serum tau protein levels again were significantly higher in the poor outcome group than those in the good outcome ($p = 0.007$) and control groups ($p = 0.006$). *Conclusions:* The present findings indicate serum tau protein levels measured on postnatal days 3 and 7 can predict neurological prognosis following neonatal asphyxia.

Keywords: Tau protein; Neonatal asphyxia; Hypoxic–ischemic encephalopathy; Neurological outcome

1. Introduction

Neonatal asphyxia is a common cause of hypoxic–ischemic encephalopathy (HIE) in newborns [1]. The neurological prognosis for neonatal asphyxia typically is determined by clinical measures that include the Apgar score, umbilical artery blood pH (UA-pH), imaging studies, and electroencephalogram [2–9]. It has been reported that a low UA-pH can predict neurological outcome after neonatal asphyxia. Even so, UA-pH is not always measured in neonates due to its expense, thus the effectiveness of UA-pH as a neurological outcome measure has yet to be determined [10].

Tau protein is a microtubule-associated protein that is necessary for cytoskeleton structure and axonal transport [11–14]. Tau protein, present in both neurons and oligodendrocytes, is found primarily in axons [14]. Elevated tau protein levels in cerebrospinal fluid (CSF) or serum can indicate neuronal injury, traumatic brain injury, or central nervous system diseases such as acute

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encephalopathy or acute ischemic stroke [15–18]. Few studies have examined serum tau protein levels in either injured or healthy neonates [19,20]. To the best of our knowledge, only one study has examined serum tau protein levels in neonatal asphyxia [21]. Here, we examine serum tau protein levels in neonatal asphyxia to determine whether this measure can predict neurological outcome.

2. Patients and methods

The Institutional Review Board of Yamaguchi University Hospital (H19-83-2) approved the study protocol. Informed consent was provided by the parents of study participants.

2.1. Neonatal asphyxia

The study participants included 19 neonates (8 boys, 11 girls; mean gestational age: 38.4 weeks; mean birth weight: 2856 g) that were admitted to the neonatal intensive care unit (NICU) between November 2008 and October 2010 with neonatal asphyxia (Apgar score <7 points at 1 min). We divided the neonates with neonatal asphyxia into 2 groups depending on whether they were with (poor outcome group, group A, $n = 3$) or without neurological sequelae (good outcome group, group B, $n = 16$) (Table 1). Pediatric neurologists determined the neurological outcome for these 19 neonates by performing an evaluation when they were 12 months old. All 3 patients in group A had severe spastic tetraplegia, and 1 patient (patient no. 3) also had west syndrome (Table 2).

2.2. Controls

The study participants included a control group comprised of 19 newborns (9 boys, 10 girls; mean gestational age, 36.7 weeks; mean birth weight, 2741 g) without neonatal asphyxia (Apgar score >6 points at 1 min). The comorbid conditions of the controls included low-birth weight ($n = 9$), newborn transient tachypnea ($n = 2$), Cesarean section delivery ($n = 7$), and hypoglycemia ($n = 1$). The controls showed no evidence of poor neurological outcome when they were 12 months old.

2.3. Methods

Umbilical artery (UA) blood samples were routinely obtained from study participants through a doubly clamped segment of the umbilical cord and collected into heparinized 5-ml syringes. From these samples, we measured blood gas concentrations and pH. Serum samples were collected during routine blood examinations, which were performed as part of the normal medical care on postnatal days 0, 3, and 7. Blood and serum samples were frozen and stored at −80 °C until the assay was performed. Serum tau protein levels were quantified using an enzyme-linked immunosorbent assay (ELISA) kit (The Invitrogen Human Tau (Total) kit, Invitrogen Co., Camarillo, CA, USA). Apgar scores were determined for each participant at 1 and 5 minutes after birth.

2.4. Statistical analysis

We conducted the Smirnov–Grubbs' test to determine whether the highest value in the group A was a significant outlier from the rest. We conducted with a Kruskal–Wallis analysis of variance to examine the serum tau protein levels among the 3 groups, because assumptions of normality of the distribution or homogeneity of variances were not verified. As more detailed examination, using the Mann–Whitney U test, we analyzed the defferences between two groups. Speaman's correlation analysis was used to study the relationship between serum protein tau levels and Apgar scores. In all statistical tests, p-values less than 0.05 were considered significant.

3. Results

Serum tau protein levels are presented in Fig. 1 and Table 3. The highest value of tau protein on postnatal day 3 in group A (21,579.3 pg/mL) was not a significant outlier, and the highest value of tau protein on postnatal day 7 in group A (23,022.4 pg/mL) was not a significant

Table 1
Clinical characteristics of the subjects.

Characteristic	Group A ($n = 3$)	Group B ($n = 16$)	Group C ($n = 19$)
Gestational age (weeks)	40.0 ± 1.0	38.1 ± 2.4	36.7 ± 2.1
Birth weight (g)	3168.0 ± 305.4	2799.1 ± 464.5	2741.3 ± 693.4
Gender			
Male	3	5	9
Female	0 (0)	11	10
1-min Apgar score <7	3 (100.0)	16 (100.0)	0 (0.0)
5-min Apgar score <7	3 (100.0)	8 (50.0)	0 (0.0)

Values are means ± SD or n (%). Group A = poor outcome patients with asphyxia; group B = good outcome patients with asphyxia; group C = control meonates.