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# The Usefulness of Routine Liver Function Tests in the Discrimination of Extrahepatic Biliary Atresia from Physiologic Jaundice in the Early Neonatal Period

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***Summary.*** **Results of routine liver function tests performed prior to Kasai's operation within 12 weeks after birth in 50 patients with extrahepatic biliary atresia during 1981 to 1992 were retrospectively analyzed. Thirty neonatal patients without cholestatic disease served as the control group. Total bilirubin, direct bilirubin and gamma-glutamyl transpeptidase levels were significantly different between the extrahepatic biliary atresia and control groups within 1 week after birth (16.1±3.2 mg/dl vs. 11.6±4.7 mg/dl, 4.6±2.6 mg/dl vs. 0.6±0.2 mg/dl, 701±228 IU/1 vs. 56±21 IU/1 respectively). Conversely, no differences were observed between them in the levels of aminotransferases within 2 weeks after birth. These data suggest that no hepatocellular damage occurs at least 2 weeks after birth in extrahepatic biliary atresia, and that the determination of bilirubin and gamma-glutamyl transpeptidase levels within 1 week after birth enable us to distinguish patients with extrahepatic biliary atresia from physiologic jaundice during this period.**

## INTRODUCTION

A number of reports concerning the results of routine liver function tests (LFTs) of extrahepatic biliary atresia (EHBA) have been published.[1-4] Although early definitive treatment of EHBA has been claimed,[5-9] only 40% of the cases received radical operation before 2 months of age, even in Japan.[10] Hence, there have been few reports describing the changes in LFTs of EHBA during the neonatal period.[14] A knowledge of the time-course changes in LFTs, especially in the neonatal period, would accordingly contribute to facilitating early differentiation of EHBA in infantile cholestatic diseases. Moreover, it might also provide important information relevant to establishing the etiology and pathogenesis of EHBA. Toward these ends, we reviewed the changes in the results of routine LFTs performed in the early stage immediately following birth in our patients with EHBA.

## PATIENTS AND METHODS

Between 1981 and 1992, 55 infants with EHBA were treated in the Niigata University Hospital and Yamagata University Hospital. All underwent a Kasai operation between 18 and 186 days after birth (median 66 days). The LFTs of 50 infants within 12 weeks after birth were investigated; the parameters of this study were total bilirubin (TB), direct bilirubin (DB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGTP) and leucine aminopeptidase (LAP). These serum tests were performed as a routine examination for hyperbilirubinemia except for 2 cases associated with duodenal atresia, in whom LFTs were performed as a postoperative examination. The mean of the test values determined on days 0 to 7 after birth of each patient was expressed as the value 1 week after birth, those determined on days 8 to 14 as the value 2 weeks after birth, days 15 to 28 as 4 weeks, 29 to 42 as 6 weeks, days 43 to 56 as 8 weeks, and days 57 to 84 as 12 weeks. Only the values determined before the Kasai operation were used for evaluation. Thirty neonatal patients, serving as the control group, were admitted to our hospital during this study period to undergo only minor surgery such as perineal anoplasty

or stoma construction. The biochemical data obtained were compared between EHBA and control patients (CO) in each age group. There were no control cases after 6 weeks of age. The chronological changes in each parameter in EHBA were evaluated by performing statistical analysis between the value obtained at 2 weeks and the values later than 4 weeks. For statistical analysis of the results, a one-way analysis of variance was used. Statistical significance was set at $p<0.01$.

## RESULTS

Results of the values of each parameter (mean ± SD) at each week and the numbers of cases comprising each datum are shown in Fig. 1 to 8. TB and DB levels were significantly different between EHBA and CO in all of the ages compared. None of the direct bilirubin values exceeded 1.6 mg/dl in CO, while individual values exceeded 2 mg/dl in 1 week in all

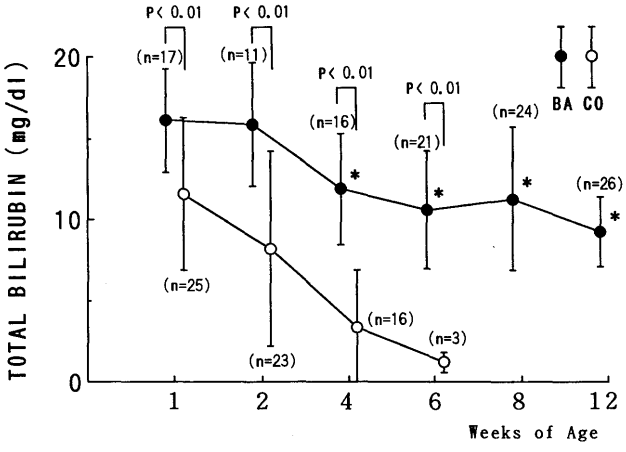


**Fig. 1.** Total bilirubin levels for each week. Data given as mean±SD (number of case examined). Asterisk; Significant difference as compared with that at 2 weeks in extrahepatic biliary atresia. BA: extrahepatic biliary atresia, CO: control.

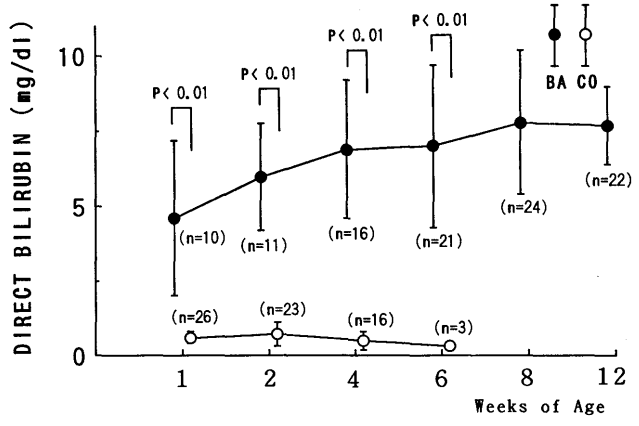


**Fig. 2.** Direct bilirubin levels for each week. Data given as mean±SD (number of case examined). BA: extrahepatic biliary atresia, CO: control.

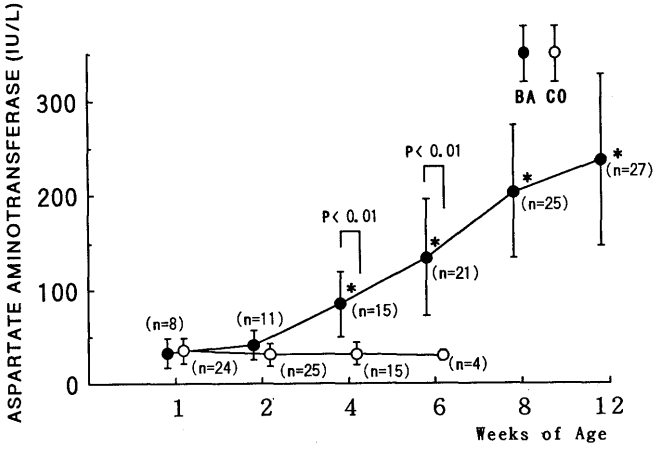


**Fig. 3.** Aspartate aminotransferase levels for each week. Data given as mean±SD (number of case examined). Asterisk; Significant difference as compared with that at 2 weeks in extrahepatic biliary atresia. BA: extrahepatic biliary atresia, CO: control.

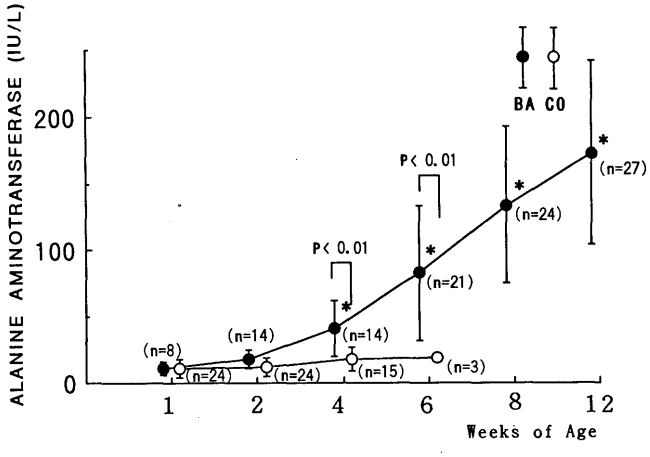


**Fig. 4.** Alanine aminotransferase levels for each week. Data given as mean±SD (number of case examined). Asterisk; Significant difference as compared with that at 2 weeks in extrahepatic biliary atresia. BA: extrahepatic biliary atresia, CO: control.

patients with EHBA. A maximum level of TB was observed 1 week after birth, and thereafter the level gradually decreased in EHBA in a manner similar in CO. On the other hand, the level of DB gradually increased with time in EHBA. The level of TB at 2 weeks was significantly higher than that seen later than 4 weeks, but there was no significant difference between the levels of DB at 2 weeks and thereafter (Fig. 1 and 2).

No notable differences were seen between EHBA and CO in the levels of AST and ALT at 1 and 2 weeks (Fig. 3 and Fig. 4). Later than 4 weeks after birth, however significant differences arose between EHBA and CO. In EHBA, the AST and ALT levels continued to increase with time, and significant differences became apparent between the levels at 2 weeks and thereafter.

The LDH level at 1 week was significantly low in EHBA as compared with that in CO, and thereafter no significant differences were seen at any week.

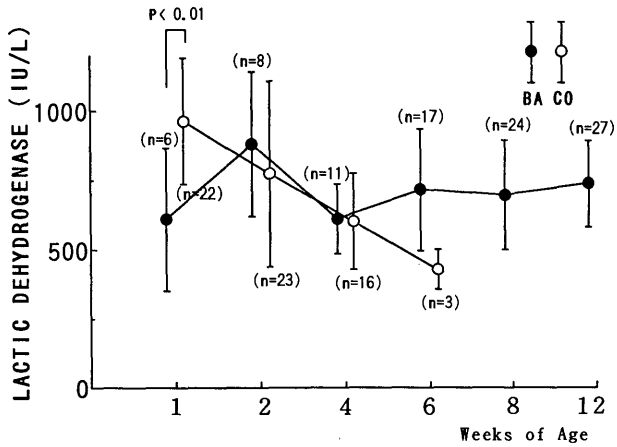


**Fig. 5.** Lactic dehydrogenase levels for each week. Data given as mean±SD (number of case examined). BA: extrahepatic biliary atresia, CO: control.

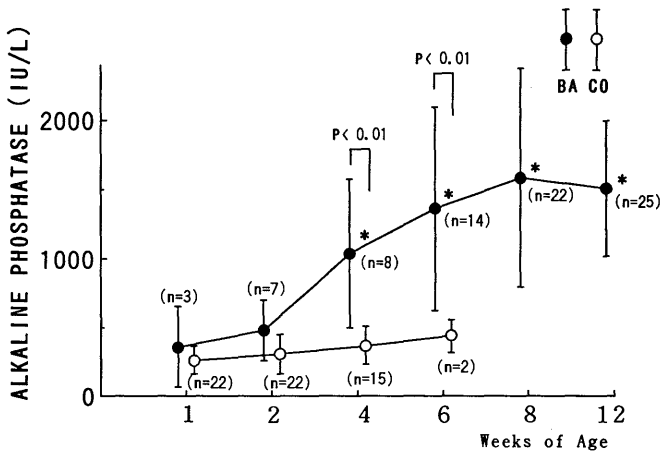


**Fig. 6** Alkaline phosphatase levels for each week. Data given as mean±SD (number of case examined). Asterisk; Significant difference as compared with that at 2 weeks in extrahepatic biliary atresia. BA: extrahepatic biliary atresia, CO: control.

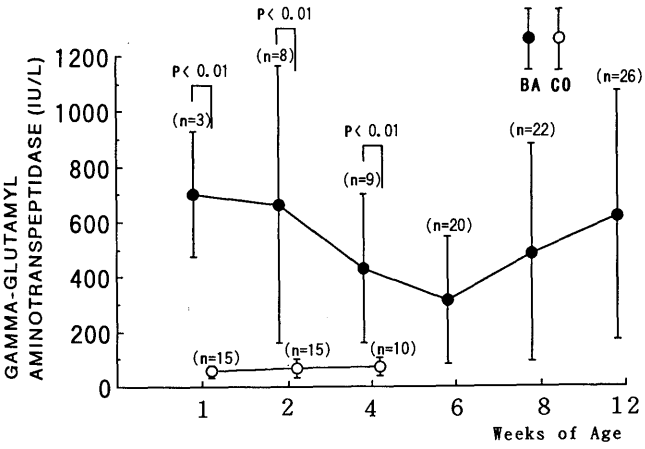


**Fig. 7.** Gamma-glutamyl aminotranspeptidase levels for each week. Data given as mean±SD (number of case examined). Asterisk; Significant difference as compared with that at 2 weeks in extrahepatic biliary atresia. BA: extrahepatic biliary atresia, CO: control.

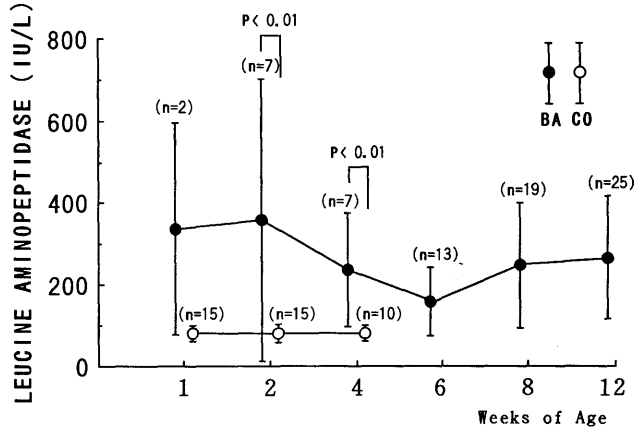


**Fig. 8.** Laucine aminopeptidase levels for each week. Data given as mean±SD (number of case examined). BA: extrahepatic biliary atresia, CO: control.

Additionally, no significant age differences in EHBA were observed (Fig. 5).

No difference was detectable between EHBA and CO in the level of ALP at 1 and 2 weeks, but a significant difference was observed at 4 weeks. In EHBA, the ALP level gradually increased with time, and there were significant differences between the levels at 2 weeks and thereafter (Fig. 6).

The GGTP levels were significantly different between EHBA and CO in every week examined. In EHBA, a maximum level was observed 1 week after birth; this level then gradually decreased to bottom out at 6 weeks, and thereafter increased with the passage of time. However, there were no significant differences at any week because of considerable variation among individuals (Fig. 7).

The LAP level was significantly different between EHBA and CO at 4 weeks. The time-course change in LAP in EHBA was similar to that of GGTP (Fig. 8).

## DISCUSSION

Numerous articles regarding biochemical studies of EHBA have been published. Although the purpose of most of these studies has concerned the search for a reliable method for the early diagnosis of EHBA, none of the authors has described changes in routine biochemical tests occurring within 1 month after birth.[1-4] Though the results reported here have been derived in retrospective fashion and consist of only routine liver function tests, the present data demonstrate clear changes in LFTs in a serial manner beginning immediately after birth.

Aminotransferase activities are known to be the indicator of hepatic cell damage. In this study, both AST and ALT remained in the normal range for 2 weeks after birth in EHBA. In 8 cases, whose AST and ALT were examined within 1 week after birth, the maximum value in individual data was 54 and 21 IU/l, respectively, both being within the normal range for this age.[11] Furthermore, in 3 of these 8 cases, the common bile duct was confirmed to be absent at surgery, which indicated that the EHBA was completed before birth. This result suggests that no hepatic cell damage occurs for at least 2 weeks after birth in EHBA regardless of the completion of the obliterated process in the extrahepatic duct at birth. As is well known, many hepatic functions are carried out for the fetus by the maternal liver, which serves as the route of elimination of metabolic end products that may cause liver damage.[12] Thus, hepatic cell damage is considered to be absent or minimal just after birth in EHBA even if the bile duct atresia has been completed in the prenatal period. More specifically, hepatic cell damage in EHBA develops after birth as the result of duct obstruction.

The reason for the significantly low level of LDH in EHBA at 1 week remains unclear. The normal range of LDH during the neonatal period is said to be very broad,[11] and in support of this, there was considerable variation in the LDH level among individuals in this study.

The TB level in EHBA was maximum at 1 week after birth and significantly higher than that in CO, and thereafter it gradually decreased in a manner similar to the change of "physiologic jaundice" in the neonates. In contrast, the DB level in EHBA gradually increased with time. The individual values of DB exceeded 2 mg/dl within 1 week in all patients with EHBA, while none of the individual values exceeded 1.6 mg/dl in CO. Half of present patients with EHBA received phototherapy for hyperbilirubinemia in the early neonatal period; therefore, if DB was measured during phototherapy, half of the patients with EHBA should have been screened out in this period.

Controversy has persisted concerning the utility of serum GGTP levels in the preoperative diagnosis of EHBA.[13-19] GGTP levels were revealed to be significantly higher in EHBA than those in intrahepatic cholestasis, but overlaps were evident between the two groups in most series.[13-17,19] Present results also showed a significantly high level of GGTP in EHBA, but there were 5 cases (13%) whose GGTP levels were below 200 IU/l. The GGTP level was extremely high at 1 week after birth and then gradually decreased to a nadir at 6 weeks, and thereafter it increased with time. Tazawa et al. reported similar time-course changes in GGTP in EHBA.[4] In 7 out of 8 cases whose GGTP levels were measured within 2 weeks after birth, the pattern of serial measurements of GGTP demonstrated initial high and rapid falling variations. Shore et al. confirmed that a striking elevation in serum GGTP activity was found in approximately half of healthy neonates, with the maximum being 261 IU/L.[20] However, individual levels of GGTP within 2 weeks in this study exceeded this level in 7 out of 8 cases. Though the origin of the extremely elevated serum GGTP level in early neonates in EHBA is unknown, a high GGTP level in this period may be a valid indicator in screening out patients with EHBA.

In conclusion, aminotransferase levels were within the normal range for 2 weeks after birth in EHBA. This result suggests that no hepatocellular damage occurs within at least 2 weeks after birth in EHBA.

DB exceeded 2 mg/dl within 1 week after birth in EHBA, while it did not exceed 1.6 mg/dl in any of the control cases. This result implies that the determination of DB within 1 week after birth enables us to screen out cholestatic jaundice from physiologic jaundice of the neonate. GGTP was significantly higher in EHBA than that in the controls with 2 weeks after birth, intimating the usefulness of measuring GGTP to diagnose EHBA in the early neonatal period.

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