

# Efficacy of Inchinkoto for Liver Cirrhosis in an Infant with Down Syndrome Complicated by Transient Myeloproliferative Disorder

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## Abstract

Several patients with Down syndrome complicated by transient myeloproliferative disorder may develop liver cirrhosis for which no effective therapeutic agent exists. We report the infant with Down syndrome complicated by transient myeloproliferative disorder and liver cirrhosis who was successfully treated by Inchinkoto, the Japanese herbal medicine. In the present case, Inchinkoto appeared to prevent both histological and serological aggravation of liver cirrhosis. To the best of our knowledge, this is the first report of preventive effect of Inchinkoto on liver cirrhosis, and it can be a choice of treatment for infants with Down syndrome complicated by liver cirrhosis.

## Keywords

Inchinkoto, Transient Myeloproliferative Disorder, Down Syndrome, Liver Fibrosis, Japanese Herbal Medicine

## 1. Introduction

Down syndrome (DS) is the most common chromosome abnormality. It is well known that approximately 10% of DS is complicated by transient myeloproliferative disorder (TMD) [1]. Although most cases of TMD regress spontaneously during the first 3 months of life without treatment [2], 20% - 30% develop lethal liver failure and multiple organ failure [3] [4].

Inchinkoto is a mixture of three medical herbs: *Artemisia capillaries spica*, *Gardenia fructus* and *Rhei rhizome*, and has long been used in Japan, mainly for liver disorders and jaundice [5] [6]. Several authors have claimed that Inchinkoto improves liver function and suppresses liver fibrosis in children with post-operative biliary atresia without serious side effects [6] [7]. However, efficacy of

Inchinkoto for liver cirrhosis (LC) for which no effective treatment exists is not yet determined.

Here, we report the efficacy of Inchinkoto for LC in an infant with DS complicated by TMD.

## 2. Case Description

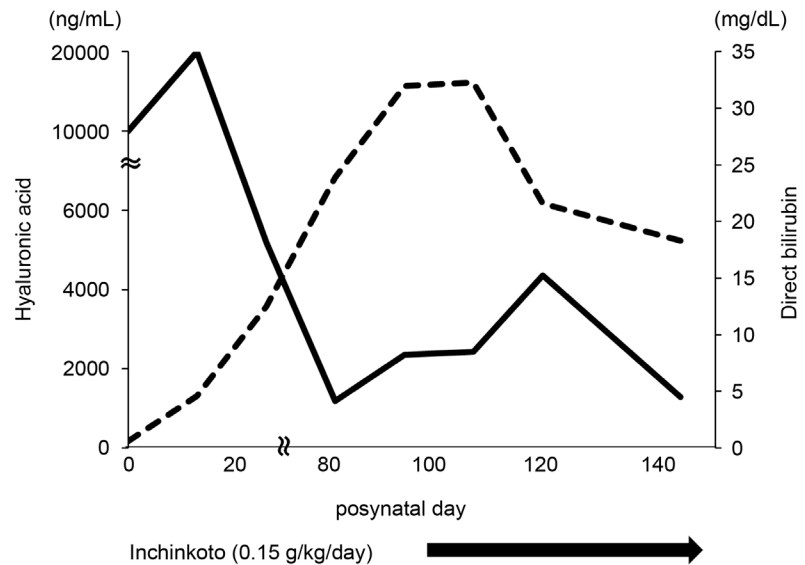
An infant was born to a 34-year-old multigravida mother. Prenatal ultrasound revealed fetal growth restriction and oligohydramnios at 32 weeks of gestation. At 34 weeks of gestation, Cesarean section under general anesthesia was urgently performed because of non-reassuring fetal status. The infant was male and his Apgar score was 3 and 8 at 1 and 5 min, respectively. His birth length was 42 cm ( $-1.1$  SD) and birth weight was 1726 g ( $-1.7$  SD). He had the phenotypic features of DS such as low-set ears, slanted palpebral fissures and saddle nose. The diagnosis of DS (21 trisomy with male karyotype) and *GATA-1* mutation (220 + 2T > C) was later confirmed by chromosomal analysis and genetic sequencing. Peripheral white blood cell count was 58,500/ $\mu$ L with 10% of blasts. Aspartate amino transferase (AST) and alanine aminotransferase (ALT) were 656 and 166 IU/L on postnatal day (PD) 0, respectively. Serum level of direct bilirubin (D-bil) was normal on PD 1, but gradually increased to 4.6 mg/dL on PD 10. Hyaluronic acid (HA) and type IV collagen, both of which are known serum biomarkers for liver fibrosis, were extraordinarily elevated on PD 1 (HA 9570 ng/mL, normal <50 ng/mL; type IV collagen 2519 ng/mL, normal <150 ng/mL, respectively). An ultrasound echocardiography detected atrial septal defect and patent ductus arteriosus necessitating no medical interventions. While he did not reveal any abnormalities of the thyroid or gastrointestinal tract, coagulation test disclosed abnormal findings on PD 0 as following: thromboplastin time 93.9 s (normal: 23 - 35 s); activated partial thromboplastin time 7.6% (normal: 75% - 130%); fibrinogen 20 mg/dL (normal: 150 - 350 mg/dL); anti-thrombin III 10% (normal: 80% - 130%).

From these results, he was diagnosed as having DS complicated by disseminated intravascular coagulation (DIC) associated with TMD and the therapeutic strategy for DIC and TMD was determined: repeated platelet transfusion and administration of fresh frozen plasma and anti-thrombin III resulted in improvement of DIC; low-dose cytarabine therapy for TMD started on PD 11 successfully decreased the number of white blood cell count and eradicated the blasts by PD 16. However, serum markers for liver functions, such as D-bil, AST and ALT continued to increase and reached 32 mg/dL, 246 IU/L and 106 IU/L, respectively on PD 98. In terms of serum biomarkers for liver fibrosis, HA was not normalized by PD 98 (2350 ng/mL) while type IV collagen returned to normal (**Figure 1**).

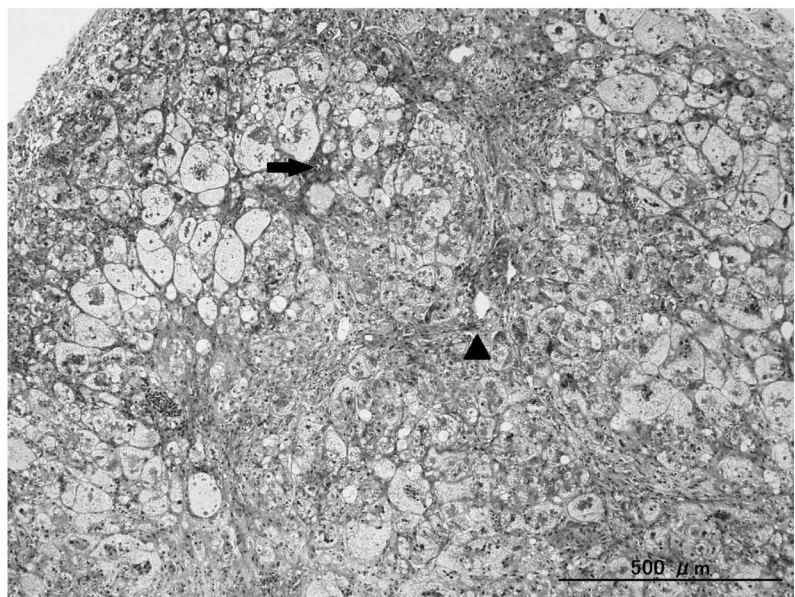
To elucidate the progressive liver failure, simultaneous biopsies on liver and bone marrow were performed on PD 76: his bone marrow showed normocellularity without blasts; in contrast, liver biopsy revealed the fibrosis in the portal vein area and hepatic lobules in addition to hyperplasia of the collagen fibers surrounding the hepatocytes (**Figure 2**). In addition, there was infiltration of lymphocytes and neutrophils, and cholestasis in the hepatocytes and bile ducts.

Based on these findings, he was diagnosed as having LC induced by TMD.

Considering its reported efficacy on liver fibrosis in children with postoperative biliary atresia [6] [7], the Japanese herbal medicine, Inchinkoto (Tsumura & Co., Tokyo, Japan) was orally administered at the dose of 0.15 g/kg-per-day) since PD 100. In parallel with the commencement of Inchinkoto, both D-bil and HA gradually decreased to 18.3 mg/dL and 1280 ng/mL, respectively on PD 144 (**Figure 1**). Improved jaundice made him possible to discharge on PD 144. Unfortunately, however, he developed fatal DIC and multiple organ failure



**Figure 1.** Serial changes in serum levels of direct bilirubin and hyaluronic acid in conjunction with administration of Inchinkoto.



**Figure 2.** Histopathological findings of liver on postnatal day on 76. Hyperplasia of the collagen fiber surrounding hepatocytes, and fibrosis (▲) in the portal vein areas and the hepatic lobules. The infiltration of lymphocytes and neutrophils (→), and cholestasis in the hepatocytes and bile duct.

triggered by severe bacterial infection and died on PD 202. It is worthy of special mention that the autopsy findings on liver disclosed no remarkable progressive changes of LC compared to those on PD 76.

### 3. Discussion

Inchinkoto has long been used to treat various liver disorders in eastern Asia such as Japan and China [5] [6] [7] [8] [9]. Iinuma, *et al.* reported that Inchinkoto might have a protective and antifibrotic effect for the liver of children with biliary atresia [6] [7]. Though the precise mechanisms of its action on the liver diseases remain unknown, it can be speculated as following: 1) inhibition of hepatocyte apoptosis induced by transforming growth factor- $\beta$ 1 [10]; 2) inhibition of the production of inflammatory cytokines and inducible nitric oxide synthase [11] [12]; and 3) direct suppression of liver fibrosis [13]. Despite the promising effects on diverse liver diseases without serious adverse effects, to the best of our knowledge, Inchinkoto has not previously been given to patients with LC characterized by diffuse nodular regeneration surrounded by fibrous bands [14].

In the present case, it appeared that Inchinkoto prevented the development of fibrosis in LC because D-bil and HA remarkably improved in parallel with commencement of its oral administration. The finding that postmortem liver specimen did not show any progression of fibrotic change compared to biopsy specimen may further support the antifibrotic effect of Inchinkoto on LC. Though measurements of cytokines which may link Inchinkoto with antifibrotic action on liver were not determined, we speculate that Inchinkoto suppressed the production of transforming growth factor- $\beta$ 1 and inflammatory cytokine. While low-dose cytarabine to treat TMD occasionally not only induces hematological regression but also improves liver fibrosis in some cases [15], these did not fit into our case.

TMD is a well-known hematopoietic disorder that occurs as a complication in approximately 10% of children with DS [5]. Although TMD is a benign disease in most cases, some patients with TMD develop severe liver failure and/or multiple organ failure. Our patient had the *GATA-1* mutation (220 + 2T > C), which is known to cause a lack of expression of the full-length *GATA-1* protein [16]. The prevalences of *GATA-1* mutation in DS have been reported to be 97.3% in patients with TMD and 89.2% in those with acute megakaryoblastic leukemia, respectively [17]. Thus, *GATA-1* mutation is thought to play an important role in the pathogenesis of TMD and acute megakaryoblastic leukemia [18]. Interestingly enough, it has been recently demonstrated that *GATA-1* expression even enhances the expansion of fetal megakaryocytic precursors, resulting in hepatic fibrosis in a mouse model [19]. Our case presented abnormally high levels of serum HA and type IV collagen even on PD 1. Taken together, we suspect that TMD and liver fibrosis induced by somatic *GATA-1* mutation had started in utero.

### 4. Conclusion

In conclusion, we firstly report the promising efficacy of Inchinkoto for LC for

which no effective treatment currently exists except liver transplantation. We therefore believe that Inchinkoto can be a choice of treatment for infants with DS complicated by TMD and LC.

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## Conflicts of Interest Statement

All authors have declared that they have no conflicts of interest.

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## Abbreviations

TDM	Transient myeloproliferative disorder
DS	Down syndrome
AST	Aspartate amino transferase
ALT	Alanine aminotransferase
D-bil	Direct bilirubin
HA	Hyaluronic acid
DIC	Disseminated intravascular coagulation



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