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The use of fine-needle aspiration biopsy in detection of acute rejection in children after liver transplantation

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Abstract Diagnosis of acute rejection after liver transplantation is based mainly on clinical signs and the liver core biopsy findings. In this study we retrospectively analyzed our data on the routine use of fine-needle aspiration biopsy (FNAB) after 63 pediatric liver transplantations. A total of 824 FNABs was taken during the postoperative hospitalization, with a mean of 13 biopsies per patient. Forty-nine acute rejection episodes were diagnosed and treated after 39 transplantations (62%). The FNAB analysis detected rejections often before clinical signs. At the time of rejection diagnosis, fever was present in 38% of the patients, and serum bilirubin and alanine aminotransferase were elevated in only 19% and 13%, respectively. The rejections responded well to oral methylprednisolone, and lymphoglobulins were needed in only two episodes (4%). The results indicate that FNAB is a safe and sensitive method for the diagnosis and follow up of acute cellular rejection in pediatric liver recipients.

Keywords Fine-needle aspiration biopsy · Liver transplantation · Acute rejection · Children

Introduction

Patient and graft survivals have improved in pediatric liver transplantation with better patient selection, anesthesia and intensive care unit treatment, surgical techniques and immunosuppressive therapy. Yet acute rejection is a major problem and possibly a risk factor for chronic rejection [13, 16]. Acute rejection occurs in over half the patients undergoing liver transplantation [4]. In a report by Newell and co-workers 8% of acute rejections among children with primary transplants ended in graft loss [17]. Similarly, 11% of the rejections were irreversible in children with liver re-transplants [17]. Irreversible rejections may be caused by a delay in diagnosing a rejection episode. The diagnosis of liver allograft rejection according to clinical signs is difficult, as all symptoms and signs are unspecific and the clinical findings in the early phase of mild acute rejection are often absent [3, 10].

Liver core needle biopsy is the most widely accepted method for diagnosing acute rejection [3, 7]. Although the process of taking a core biopsy is considered safe, complications are still seen [11, 15]. The procedure also remains unpleasant for the patient and requires general anesthesia in children. Compared with core biopsy, fine-needle aspiration biopsy (FNAB) is less traumatic and may be repeated safely on a daily basis even in children with suboptimal liver function [10]. A good correlation between FNAB and core needle biopsy in the diagnosis of acute rejection of the hepatic graft has been reported [10, 11].

In this study we retrospectively analyzed our data on the use of protocol FNAB in pediatric liver recipients after 63 transplantations between 1987 and 1999. The results indicate that FNAB is a sensitive and safe method for diagnosing follow-up of acute cellular rejection in children after liver transplantation.

Patients and methods

Patients and medication

The patients included 54 children who underwent 63 liver transplantations at the Hospital for Children and Adolescents, University of Helsinki, between October 1987 and December 1999. Fifteen of the transplants were full size and 48 were reduced size. Nine patients received ABO incompatible grafts. Biliary atresia ($n=21$) tyrosinemia (9), and hepatic tumor (8) were the main indications for transplantation. Nine re-transplantations were performed. The patient characteristics are given in Table 1.

All children received triple drug immunosuppression with methylprednisolone, azathioprine and cyclosporin A after the operation as reported previously [19]. Acute rejections were treated with an increased dose of oral methylprednisolone (3 mg/kg/day, in four doses) for 5 days. In steroid-resistant rejections antithymocyte globulin (ATG, Merieux) or OKT3 (Orthon) were used. Prophylaxis for cytomegalovirus (CMV) infection varied during the study period depending on the serological status of the recipient and donor [19]. Trimethoprim-sulfamethoxazole prophylaxis for *Pneumocystis carinii* infection was given to all patients for 1 year after transplantation.

Fine-needle aspiration biopsies

Protocol fine-needle aspiration biopsies (FNABs) were first taken on the 3rd to 5th postoperative day and repeated at 2- to 3-day intervals thereafter, and in addition whenever rejection was suspected. The technique for the aspiration procedure has been previously described [5, 10, 11]. Residents performed the biopsies at the bedside in the morning, and the results of the analyses were available in the afternoon. Only local anesthesia (Xylocaine cream) was used.

The cytological FNAB samples were prepared and analyzed according to the method described previously [8, 9]. In this method each inflammatory cell type is given a correction factor which reflects the diagnostic value of the cell type in acute rejection. Lymphoblasts, plasma cells, monoblasts and macrophages have the highest correction factor: 1.0; active lymphocytes: 0.5; granular large lymphocytes and monocytes: 0.2; and lymphocytes and polymorphonuclear cells: 0.1. The result is expressed as total corrected increment (TCI), which is a corrected sum of inflammatory cells in the FNAB from which the blood background is subtracted. Also, the number of lymphoblasts (blast count) in the sample is counted. The morphological or cholestatic changes in the parenchymal cells are also assessed [11]. A description of the findings is included in the cytological analysis. The diagnosis of an acute rejection depended both on the FNAB results and clinical findings. The signs for acute rejection are appearance of lymphoblasts and increase of lymphocytes in the graft. A TCI value >3.0, together with lymphoblasts, was considered to be immunoactivation associated with rejection [11].

Viral infections, especially CMV infection, often cause differential diagnostic problems in transplant patients, and CMV infection can induce a generalized immunoactivation in the patient [12]. This, however, is usually seen both in blood and in the graft, while in acute rejection it is mainly located in the graft [12].

Core needle biopsies were taken only when steroid resistant rejections were suspected or when the histological assessment of the graft was needed.

Table 1. Patients and outcome after 63 liver transplantations

Patients (*n*)	54
Male/female (*n*)	28/26
Transplantations (*n*)	63
<2 Years (*n*)	28
≥2 Years (*n*)	35
Median age at transplantation (range) (years)	2.68 (0.38–16.32)
Median time of hospitalization (range) (days)	34 (1–99)
Re-transplantations[a] (*n*)	9
Deaths	12
Multi organ failure	3
Portal vein thrombosis	1
Portal vein thrombosis and pneumonia	1
Portal vein and inferior vena cava thrombosis and concomitant rejection	1
Hepatic artery thrombosis	1
Liver failure and cerebral bleeding	1
Cerebral insult	3
Transplant nonfunction	1

[a]Five because of hepatic artery thrombosis and four due to chronic rejection

Methods

Medical records were reviewed retrospectively for all patients, and data concerning the postoperative hospital stay were collected. Clinical and laboratory data, as well as the findings of the abdominal ultrasound investigations, FNABs and core needle biopsies, were recorded. The diagnosis of CMV infection was based on CMV antigenemia test and viral cultures [10]. The diagnosis of the Epstein-Barr and other viruses was based on serological findings (elevated IgM-antibody titers). The children were divided into two groups based on their age at transplantation (<2 years and ≥2 years).

The FNAB findings were correlated to signs associated with acute rejection: serum total bilirubin (S-Bil), serum alanine aminotransferase (ALT) and fever. The increase in S-Bil and ALT concentrations were defined as standard deviations (SDs), and values over two SDs were considered significant. The SD values were calculated from the daily measurements in those patients who did not have acute rejections or other major complications (24 patients). The SD values were 7 μmol/l for S-Bil and 13 U/l for ALT. Fever was defined as a body temperature ≥38 °C.

For statistical analysis an unpaired two-tailed Student's t test was used. A P value < 0.05 was considered statistically significant. The study was approved by the ethical committee of the Hospital for Children and Adolescents, University of Helsinki.

Results

Outcome

Sixty-three liver transplantations were performed on 54 children. Of these transplantations, 48 (76%) had favorable outcomes, and the patients were send home with

a well-functioning graft after a mean hospitalization of 34 days. The major complications included thrombosis of the hepatic artery (seven episodes) and portal vein (four). Overall, 12 children died for various reasons during hospitalization (Table 1). Six were < 2 years of age. One of the patients had acute rejection and thrombosis of the inferior vena cava and portal vein before death. Based on the biopsy and clinical findings as well as the autopsy material, acute rejection was not involved in the deaths of the other 11 patients.

Biopsies and rejections

The grafts were followed by protocol fine-needle biopsies during hospitalization. A total of 824 FNABs was taken after the 63 operations, with a mean of 13 biopsies per patient (Table 2). Only 58 (7%) samples were inadequate and could not be analyzed. No major complications occurred. Core needle biopsies were taken only when the cytological analysis of FNAB was not informative enough. In total, 12 core needle biopsies were taken on ten patients. Only three of these biopsies were taken to verify the FNAB finding (Table 2).

Based on the FNAB and clinical findings, 49 rejections were diagnosed and treated in 39 patients (Table 3). The median time to rejection was 11 days after transplantation (Table 3). In those nine patients who received ABO incompatible grafts, five rejections (56%) were recorded, similar to the frequency seen in patients with compatible grafts.

In total, 47 of the 49 rejections (96%) were resolved with low-dose oral methylprednisolone (3 mg/kg/day for 5 days) and were regarded as steroid sensitive. Two episodes were steroid resistant. ATG was given successfully in the first case and both ATG and OKT3 were used in the other. The latter patient, however, died on the 44th postoperative day, from rejection and thrombosis of the inferior vena cava.

FNAB findings

FNAB findings not leading to rejection therapy

The distribution of TCI values and blast counts in 612 FNAB samples, which did not lead to rejection therapy, is shown in Table 4, side A. A completely normal finding (TCI < 3.0 and blast count < 3) was observed in 71% of the samples, and mild immunoactivation (TCI value of 3.0–5.0 and blast count ≤ 5) in 9% of the biopsies.

A clear immunoactivation (TCI value > 3.0 and blast count > 5) was seen in 26 samples (4.2%) which did not lead to rejection therapy. In most cases, an ongoing infection was regarded as responsible for the cytological finding (Table 5).

FNAB findings leading to rejection therapy

The TCI scores and blast counts in 49 FNAB samples taken on the 1st day of rejection therapy are shown in Table 4, side B. The mean TCI value and blast count in these samples were 6.3 and 25, respectively. A clear immunoactivation (TCI > 3.0 and blast count > 5) was observed in 73% (36/49) of these samples. All samples leading to rejection therapy had a TCI value > 3.0, and in those cases with only mild immunoactivation in FNAB six of eight patients had clinical signs of rejection (Table 5).

In two-thirds of the episodes (34/49), rejection therapy was started on the first day of a TCI value > 3.0. In the rest of the episodes, two to five FNAB samples taken on consecutive days showed immunoactivation before the commencement of rejection therapy.

FNAB findings after rejection therapy

Forty-six control FNABs were taken after the 5-day course of rejection therapy. TCI and blast count both

Table 2. FNAB and core needle biopsies from 54 children taken during hospitalization after 63 liver transplantations. *n* Number of transplantations

Biopsies	Recipient age		All $n=63$
	< 2 Years $n=28$	≥2 Years $n=35$	
FNAB			
Total number	381	443	824
Mean number per patient (range)	13.6 (0–27)	12.6 (0–28)	13.1 (0–28)
Number of representative samples (% of all)	362 (95)	404 (91)	766 (93)
Core needle biopsies			
Total number (patients)	5 (5)	7 (5)	12 (10)
Indications			
Verification of FNAB	1	2	3
Steroid-resistant rejection	1	0	1
Graft dysfunction	1	5	6
Vascular complications	2	0	2

Table 3. Acute rejections in 54 children during postoperative hospitalization after 63 liver transplantations. *n* Number of transplantations

Rejections	Age at transplantation		All $n=63$
	<2 Years $n=28$	≥2 Years $n=35$	
Total no. (frequency)	29 (1.0)	20 (0.6)	49 (0.8)
Number of patients with rejection (%)	22 (79)	17 (49)	39 (62)
No rejection	6 (21)	18 (51)	24 (38)
One rejection	17 (61)	14 (40)	31 (49)
Two rejections	4 (14)	3 (9)	7 (11)
≥Three rejections	1 (4)	0	1 (2)
Median day of rejection (range)	10 (5–51)	12 (6–67)	11 (5–67)
Outcome of rejection			
Reversed with steroids	28 (97%)	19 (95%)	47 (96%)
Steroid resistant rejections	1 (3%)	1 (5%)	2 (4%)
Graft loss due to rejection	1 (4%)	0	1 (2%)

Table 4. TCI and blast counts in 661 FNAB samples from 54 patients after 63 liver transplantations (samples taken during rejection treatment are excluded). *A.* Diagnostic samples not leading to rejection therapy, *B.* samples taken on the 1st day of rejection therapy

A. No rejection (612 samples)				Total number		B. At diagnosis of rejection (49 samples)				Total number	
Blasts/preparation	TCI					Blasts/preparation	TCI				
	<3	3–5	>5				<3	3–5	>5		
≤2	435	20	4	459	75%	≤2	0	1	2	3	6%
3–5	72	36	3	111	18%	3–5	0	7	3	10	20%
6–10	13	18	2	33	5%	6–10	0	9	5	14	29%
>10	3	3	3	9	1%	>10	0	1	21	22	45%
Total number	523	77	12			Total number	0	18	31		
	85%	13%	2%				0%	37%	63%		

normalized during therapy in 78% of the episodes. The mean TCI score and blast count after therapy were 1.9 and 3.2, respectively. In six control FNABs, both an elevated TCI value (>3.0) and blast count (>5) was found. In four cases only TCI remained elevated, and in one only the blast count remained high. Two of these 11 cases were regarded as steroid-resistant rejections; in seven episodes the findings normalized in the following samples, and in two cases steroid therapy was repeated.

FNAB findings during viral infections

Twenty-two patients had a CMV infection during hospitalization. Two episodes of CMV hepatitis, one of CMV pneumonitis and two febrile diseases were recorded. All other episodes were mild CMV viremias. Of these 22 patients, 15 (68%) had one or more rejection, compared with 61% (25/41) of the children with no CMV manifestations.

The FNAB samples remained normal (TCI <3.0) in 74% of the 92 samples taken during the CMV infection. In 26% of the episodes a various degree of immunoactivation was present (Table 6). In 38 of the 92 (41%) samples, CMV or other viral infection was suggested in the description of the FNAB findings.

Only two cases of adenovirus infection were diagnosed during the follow-up. While strong immunoactivation (TCI: 5.2 and blast count: 40) was seen in one episode, the FNAB findings remained normal in the other.

FNAB findings during vascular complications

The FNAB findings during hypoxia caused by hepatic artery thrombosis were quite normal. Thirty-nine FNABs were taken and of these four indicated rejection treatment. In the four patients who experienced portal-vein thrombosis (one with thrombosis of the inferior vena cava) two rejection episodes were diagnosed. In total, 94% of the FNAB samples taken during vascular complications were normal, and 6% showed mild immunoactivation (Table 6).

Liver cells

Possible changes in hepatocytes were also evaluated in the cytological FNAB samples. Mild-to-moderate de-

Table 5. TCI scores and blast counts in 653 FNAB samples after 63 liver transplantations in 54 children

FNAB findings	Total	Rejection therapy started		Comments
		No	Yes	
No cytological rejection				
No immunoactivation (TCI < 3)	523	523	0	
Mild immunoactivation (TCI 3–5, blast count ≤ 5)	64	56	8	Clinical findings in the eight episodes where rejection therapy was started: Elevated S-Bil and fever (2), elevated ALT and fever (1), elevated ALT and S-Bil (1), fever (2), no clinical signs (2)
Cytological rejection				
Moderate immunoactivation (TCI 3–5, blast count > 5)	25	15	10	Clinical findings in the 15 episodes with no rejection therapy: CMV viremia (4), normalization of FNAB during follow up (11)
(TCI > 5, blast count ≥5)	10	5	5	Clinical findings in the five episodes with no rejection therapy: CMV viremia (4), normalization of FNAB during follow up (1)
Strong immunoactivation (TCI > 5, blast count > 5)	31	5	26	Clinical findings in the five episodes with no rejection therapy: CMV viremia (4), adenovirus infection (1)

generative changes (vacuoles) were often (78%) seen even in samples without rejection. Severe degeneration was present in 4%, and necrosis in one sample. In samples taken when rejection diagnosis was set, mild-to-moderate cytological changes were present in 84%. Cholestasis was a common finding in the biopsies. It was observed in samples without and with rejection in 50% and 55% of the samples, respectively. However, severe cholestasis was rare (in 6% of both sample groups).

Clinical signs of rejection

Fever

Fever (temperature ≥38 °C) was recorded in 38% of the rejections on the 1st day of rejection therapy, and in 45% of the episodes overall (Table 7). Fever with normal FNAB findings occurred on 72 occasions. Thirty-nine of these episodes were most probably due to infections (13 viral, 26 bacterial), four occurred with vascular complications and 29 were of unknown origin.

Serum ALT

ALT significantly increased (> 2 SD; 1 SD = 13 U/l) in only six out of 46 episodes (13%) at the time of diagnosis of acute rejection by FNAB (Table 7). In four (8%) occasions ALT increased before the FNAB findings had indicated rejection. Overall, a rise in ALT was seen in 35% of the rejections. The median rise was 10.5 SD (136 U/l). No relationship between the rise in ALT and the TCI value or blast count at the diagnosis of rejection was seen.

Besides rejections, a significant increase in ALT concentration occurred on 39 occasions. In these cases the FNAB findings remained normal. The probable reasons for the ALT elevation were vascular complications (six episodes), infections (ten cases of CMV infection, one viral gastroenteritis, four septicemia, and

Table 6. FNAB findings in different clinical events after the 63 liver transplantations in 54 children

Clinical findings	No. of samples	FNAB			
		No immunoactivation (TCI < 3) (%)	Mild immunoactivation (TCI > 3, blast count < 5) (%)	Moderate immunoactivation (TCI 3–5, blast count > 5) (%)	Strong immunoactivation (TCI > 5, blast count > 5) (%)
Normal	468	87	10	30.2	
Rejection	49	0	27	20	53
Vascular complication	54	94	6	0	0
CMV infection	92	74	16.3	5.4	4.3

one bacterial pneumonia), abscesses (one subphrenic, one intrahepatic) and multi-organ failure (one case). The cause could not be defined in 14 episodes.

Total serum bilirubin

A significant increase in the S-Bil concentration (14 μmol/l above the baseline) at the time of rejection diagnosis was seen in 19% of the episodes (Table 7). During rejection the rise was present in 24% of the episodes. A rise over 2 SD for other reasons was recorded in 33 occasions. The probable reasons for the elevations were vascular complications (eight cases), infections (six) and multi-organ failure (four). The cause could not be defined in 15 episodes.

Combination of clinical signs

Both fever and elevated ALT were observed in only one of the episodes at diagnosis of rejection. Fever and a rise in S-Bil was seen in three instances, and on one occasion an increase in bilirubin and ALT concentration was observed. The FNAB findings in episodes with or without clinical signs of rejection did not differ markedly ($P > 0.05$).

Comparison of the diagnostic parameters is presented in Table 8. The significant finding was that the sensitivity and positive predictive values were clearly higher in FNAB than clinical signs.

Comparison of the age groups

Small children had more acute rejections than older ones. Rejections occurred in 79% of the children < 2 years of age and in 49% of older children (Table 2). FNAB findings were quite similar in the two age groups at diagnosis of rejection. The median TCI was 5.7 and 5.5, respectively, and the median blast count 10 in both age groups. One steroid-resistant rejection was seen in both age groups.

Serum ALT concentration was increased in only 4% of the small children at the time of diagnosis of rejection (Table 7). In the older children the rise occurred in 26% of the episodes. During rejection an elevation of ALT was seen in 31% and 50%, respectively ($P > 0.05$). No major difference in the rise of S-Bil between the two age groups was seen: significant increase occurred in 20% and 16% of the cases at the time of diagnosis (Table 7). On the other hand, rejection induced fever more often in the younger children than in the older ones (Table 7). Fever was recorded in 50% and 21% of the children at diagnosis of rejection, and in 56% and 30% of the patients during rejection, respectively ($P < 0.05$).

Discussion

This is the first report where the use of FNAB for diagnosing acute rejection has been systematically studied in pediatric liver recipients. The results of the 824 biopsies indicate that FNAB is a safe and sensitive method for the diagnosis and follow-up of acute cellular rejections in all age groups.

Acute rejection is a common problem after liver transplantation and its early recognition and treatment is important [2]. The cytological analysis of FNAB samples is methodologically simple, and the results are available on the same day. The biopsy technique is easy to learn, which is supported by the fact that 93% of the samples in our material were representative. No ultra-

Table 7. Serum ALT, serum bilirubin and body temperature at diagnosis of 49 acute rejections in 54 children after 63 liver transplantations. The values were obtained on the day rejection therapy was started

Clinical finding	Recipient age		All
	< 2 Years	≥2 Years	
Serum ALT[a]			
Not elevated (< 2 SD)	26/27 (96%)	14/19 (74%)	40/46 (87%)
Moderately elevated (2–5 SD)	1/27 (4%)	1/19 (5%)	2/46 (4%)
Clearly elevated (> 5 SD)	0	4/19 (21%)	4/46 (9%)
Serum bilirubin[b]			
Not elevated (< 2 SD)	16/20 (80%)	10/12 (83%)	26/32 (81%)
Moderately elevated (2–5 SD)	2/20 (10%)	1/12 (8%)	3/32 (9%)
Clearly elevated (> 5 SD)	2/20 (10%)	1/12 (8%)	3/32 (9%)
Body temperature[c]			
< 37.0 °C	1/26 (4%)	8/19 (42%)	9/45 (20%)
37.0–37.9 °C	12/26 (46%)	7/19 (37%)	19/45 (42%)
38.0–38.9 °C	9/26 (35%)	3/19 (16%)	12/45 (27%)
≥39.0 °C	4/26 (15%)	1/19 (5%)	5/45 (11%)

[a]Unknown in three episodes
[b]Unknown in 17 episodes
[c]Unknown in four episodes

Table 8. Sensitivity, specificity and positive and negative predictive value for the FNAB analysis and the clinical findings on the day rejection was diagnosed. Rejection was defined as an episode which was treated with methylprednisolone

Clinical finding	Sensitivity	Specificity	Positive predictive value	Negative predictive value
FNAB				
TCI ≥3, blast count ≥3	0.94	0.89	0.41	0.99
TCI ≥3, blast count > 5	0.73	0.96	0.58	0.98
Elevated ALT (≥2 SD)	0.13	0.98	0.13	0.98
Elevated body temperature (≥38 °C)	0.38	0.96	0.19	0.98
Elevated S-Bil (≥2 SD)	0.19	0.97	0.15	0.98

sound guidance is needed for the procedure and only local anesthesia (Xylocaine cream) is used. One of the advantages of this procedure is its safety. Bleeding easily complicates core needle biopsies, especially in patients with thrombocytopenia and low levels of coagulation factors [14]. No major bleeding or other complications occurred in our patients after FNAB.

FNAB does not completely eliminate the need for core needle biopsies, which are still necessary when chronic or steroid-resistant rejections are suspected, or histological evaluation of the liver parenchyma is needed. In our study, core needle biopsies were taken from ten of the 63 allografts (16%). However, only three of them were taken to verify the FNAB findings.

Several studies have shown a good correlation between FNAB and core needle-biopsy findings [6, 11, 14, 18]. We did not take routine core needle biopsies and no comparison of the cytological and histological methods was possible. The FNAB findings are not completely specific for rejection. Elevated TCI values and blast counts are found in infections [10, 12]. This was also the case in our study, where a moderately elevated TCI value (3–5) was often associated with an ongoing infection. Vascular complications with liver hypoxia, however, had little effect on the FNAB findings.

The diagnosis of acute rejection is usually based on clinical signs and core needle-biopsy findings. The clinical and laboratory findings, however, lack sensitivity and specificity [3, 4]. In our patients a rise in S-Bil was seen in 44 episodes, but in only 25% of the episodes was acute rejection diagnosed. Similarly, serum ALT concentration increased markedly on 56 occasions, but the FNAB findings indicated significant immunoactivation in only 30% of the episodes. Fever occurred 93 times, but FNAB findings indicated rejection on only 21 occasions (23%). The daily FNAB samples clearly help in differentiating the cause of fever or an elevated serum ALT or S-Bil level. In our patients, half the rejection therapies were based only on the FNAB findings and had started before fever or increased serum ALT or S-Bil concentration was noticed. Thus, the protocol of using routine FNAB helps in diagnosing and treating early immunoactivation, which presumably reduces the tissue damage.

In our study the sensitivity and specificity for FNAB (TCI ≥3 and blast count ≥3) in the diagnosis of acute rejections was 94% and 89%, respectively. For a higher blast count (> 5) the sensitivity was 73% and the specificity 96%. Earlier, Kirby et al. reported a good sensitivity and specificity (76.7% and 86.9%, respectively) for FNAB in the diagnosis of acute rejection [6]. The sensitivity values for the clinical findings were clearly lower than for the FNAB analysis. These numbers, however, must be taken with some caution, since the calculations were based on the assumption that the rejection therapy was correctly started every time. Interestingly, rejection therapy was never started when TCI values were below 3.

The need for treating cellular infiltrates if they are not associated with significant graft damage has been discussed [15]. On the other hand, early diagnosis of rejection probably has an impact on the favorable outcome of rejection therapy. In total, 96% of the rejections in our patients responded to low-dose methylprednisolone and only one graft (2%) was lost because of rejection. In N. American material, 8% of primary transplants and 11% of re-transplants were lost due to rejection [17]. As more than 90% of acute rejection episodes are believed to occur within 1 month of liver transplantation, we believe these numbers can be compared [1].

Liver graft survival in small children is less favorable than in older recipients [1]. A heightened immune response in small children has been suggested. In our patients, rejection occurred more often (79%) in small children than in children over 2 years of age (49%). FNAB findings, however, were similar in the different age groups. Serum ALT concentration was increased less often in infants (4%) than in older children (26%) at diagnosis of rejection. On the other hand, small children had a fever more often than the older ones during rejection. The only transplant lost was in a patient under 2 years of age. In our patients no significant difference in the incidence or outcome of rejections, between primary transplants and re-transplants, was seen.

In conclusion, we feel that FNAB is a safe and sensitive method for the diagnosis and management of acute rejections in pediatric liver recipients.

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