Corticosteroid Therapy for Indeterminate Pediatric Acute Liver Failure and Aplastic Anemia with Acute Hepatitis

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Objective To examine the characteristics and outcomes of a multicenter patient cohort with indeterminate pediatric acute liver failure (IND-PALF) and with aplastic anemia with acute hepatitis treated with corticosteroids.

Study design Retrospective study of patients age 1-17 years with IND-PALF and aplastic anemia with acute hepatitis who presented between 2009 and 2018 to 1 of 4 institutions and were treated with corticosteroids for presumed immune dysregulation.

Results Of 28 patients with IND-PALF (median of 4.0 years of age [range 1-16] and 71% male) 71% (n = 20) were treated with 0.5-4 mg/kg/day of intravenous methylprednisolone, and 8 patients received 10 mg/kg/day followed by a taper. By 21 days postcorticosteroid initiation, 14 patients (50%) underwent liver transplantation, 13 patients (46%) recovered with their native liver, and 1 patient (4%) died. Patients who recovered with their native liver received a median of 139 days (range 19-749) of corticosteroid therapy, with a median of 12 days (range 1-240) to international normalized ratio ≤1.2. Patients with aplastic anemia with acute hepatitis (n = 6; median of 9.5 years of age [range 1-12], 83% male), received 1-2 mg/kg/day of methylprednisolone for a median of 100 days (range 63-183), and all recovered with their native liver. One patient with IND-PALF and 2 patients with aplastic anemia with acute hepatitis developed a serious infection within 90 days postcorticosteroid initiation.

Conclusions Many patients with IND-PALF or aplastic anemia with acute hepatitis that were treated with corticosteroids improved, but survival with native liver may not be different from historical reports. A randomized controlled trial exploring the benefits and risks of steroid therapy is needed before it is adopted broadly. *(J Pediatr 2019;208:23-9)*.

Pediatric acute liver failure (PALF) is a rare syndrome in which a child with no prior history of liver disease rapidly develops liver synthetic dysfunction. There are several known causes of PALF, including infectious hepatitis, drug toxicity, autoimmune liver disease, and metabolic or genetic disorders. However, in up to 40% of patients with PALF, an etiology is not determined and, thus, designated as indeterminate PALF (IND-PALF). Likely this indeterminate group includes some patients with an unidentified known etiology because of either incomplete diagnostic evaluation or lack of available clinical testing. However, recent efforts to adjudicate these cases as viral hepatitis, occult acetaminophen toxicity, or other known diagnoses have reclassified only a small percent.[1-3] By definition, children with IND-PALF lack targeted treatment strategies and are more likely to undergo liver transplantation compared with patients with a specified etiology. Growing evidence suggests that many patients with IND-PALF have liver injury driven by immune dysregulation and activation, which manifests as elevated serum soluble interleukin-2 receptor levels, peripheral blood cytopenias, and liver injury characterized by a dense CD8+ T-cell infiltrate.[4-7] A well-recognized association with IND-PALF is the development of aplastic anemia either coincident with or several months following the acute liver failure (ALF) presentation, which may be severe and require hematopoietic stem cell transplantation.[8] Notably, aplastic anemia can also occur in children with a less severe hepatic phenotype that may not meet current PALF diagnostic criteria, but who present with dramatic acute hepatitis. These children often demonstrate many of the immune-active features of IND-PALF including predominance of CD8+ T-cells in peripheral blood and/or on liver histology.[9-11]

ALF	Acute liver failure
ALT	Alanine aminotransferase
AIH	Autoimmune hepatitis
HHV	Human herpes virus
IND-PALF	Indeterminate PALF
INR	International normalized ratio
PALFSG	PALF Study Group
PALF	Pediatric acute liver failure
PCR	Polymerase chain reaction

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Based on these observations, there is a growing trend toward treatment of patients with IND-PALF and patients with aplastic anemia with acute hepatitis with corticosteroids.[7,12,13] We aim to describe the characteristics and outcomes of patients with IND-PALF and aplastic anemia with acute hepatitis treated with corticosteroids at 4 large pediatric liver transplant centers.

Methods

This is a retrospective multicenter study of children with IND-PALF or aplastic anemia with acute hepatitis who were treated with steroids. Patients presented to 1 of the 4 study institutions, Ann and Robert H. Lurie Children's Hospital of Chicago, Seattle Children's Hospital, Children's Hospital of Pittsburgh, or Children's Hospital of Philadelphia from 2009 to 2018. Potential IND-PALF cases were identified by *International Classification of Diseases, Ninth Revision* and *International Statistical Classification of Diseases, Tenth Revision* database code search for acute liver failure. Potential cases with aplastic anemia with acute hepatitis were identified by *International Classification of Diseases, Ninth Revision* and *International Statistical Classification of Diseases, Tenth Revision* database code search for aplastic anemia and hepatitis. PALF was defined using the previously published PALF Study Group (PALFSG) criteria: (1) no known evidence of chronic liver disease; (2) biochemical evidence of acute liver injury; and (3) hepatic-based coagulopathy (not corrected with vitamin K) defined as prothrombin time ≥15 seconds or international normalized ratio (INR) ≥1.5 in the presence of clinical encephalopathy, or a prothrombin time ≥20 seconds or INR ≥2.0 regardless of the presence or absence of encephalopathy.[14] Aplastic anemia with acute hepatitis was defined as (1) no known evidence of chronic liver disease; (2) biochemical evidence of acute liver injury with onset of illness within 8 weeks of presentation and alanine aminotransferase (ALT) ≥500; and (3) aplastic anemia based on peripheral blood cytopenias and hypocellular bone marrow biopsy. Cases were defined as indeterminate if no known cause for their liver disease was identified despite an age-appropriate diagnostic evaluation. A thorough diagnostic workup, as determined by review of the medical record at each individual site, was defined as including for all patients a comprehensive review of possible exposures to medications and supplements, negative testing for common infections including hepatitis B surface antigen, IgM antibody to hepatitis B core antigen, or hepatitis B virus DNA polymerase chain reaction (PCR), anti-hepatitis A virus IgM, Epstein Barr virus VCA IgM or Epstein Barr virus PCR, and herpes simplex virus IgM or herpes simplex virus PCR, and negative screening for autoimmune hepatitis (AIH) (antinuclear antibody [AA], antismooth muscle antibody [SMA], and antiliver kidney microsomal antibody [LKM] using institution-specific cut-off values for positive results).[3,15] Additional workup for patients 4 years of age and older included negative screening for Wilson disease (serum ceruloplasmin level and/or 24-hour urinary copper excretion), and for patients under 2 years of age, or those with a consistent presentation, negative screening for metabolic disease with urine organic acids and/or plasma acylcarnitine profile.[3,16]

Patients with IND-PALF and aplastic anemia with acute hepatitis who were between 1 and 17 years of age, and who were treated with corticosteroids for liver dysfunction during their hospital admission were included. Patients with aplastic anemia with acute hepatitis who were given corticosteroids specifically for treatment of aplastic anemia and not treatment of hepatitis were excluded. Therapeutic decisions including dosing and duration of corticosteroid therapy were at the discretion of the managing physicians. Chart review was conducted to collect demographic, laboratory, and outcome data, and evaluate the diagnostic workup. Information collected included age at presentation, sex, duration of illness prior to admission, duration of admission (until discharge with native liver, liver transplantation, or death), dose and duration of corticosteroid therapy, laboratory values and encephalopathy grade pre- and post-corticosteroid therapy, 21-day and 90-day outcome postcorticosteroid initiation (spontaneous recovery with native liver, liver transplantation, or death), development of aplastic anemia within 90 days pre- or postcorticosteroid initiation, and clinically significant infection within 90 days postcorticosteroid initiation (including sepsis, pneumonia, urinary tract infection, intraabdominal infection, and tissue invasive cytomegalovirus). Liver biopsy and bone marrow biopsy pathology reports were reviewed for patients who had these procedures performed prior to initiation of corticosteroid therapy. For patients with aplastic anemia with acute hepatitis who underwent stem cell transplantation, duration of steroid therapy was measured up until initiation of conditioning regimen. Additional data regarding serum biomarkers of immune activation status were collected when available, including soluble interleukin-2 receptor (sIL-2R) level, natural killer cell function (decreased/absent or normal), and peripheral blood T- and B-cell flow cytometry ratio of CD4 to CD8 T-cells (normal or ≤1.0). IND-PALF patient 21- and 90-day poststeroid initiation outcomes were compared with published historical outcomes of indeterminate patients from the initial PALFSG cohort of 348 patients.[14] This older cohort was chosen as a comparison group because children were enrolled between 1999 and 2004, prior to the use of corticosteroids as empiric therapy for indeterminate patients with PALF.

Data are reported as percentages if categorical, means ± SE if normally distributed, or median with range if not normally distributed. This study was approved by the Institutional Review Boards of the participating centers. The requirement for informed consent was waived.

Results

A total of 28 patients with IND-PALF and 6 patients with aplastic anemia with acute hepatitis were identified. Patients

Table I. Indeterminate PALF patient demographics and laboratory values at presentation and at time of corticosteroid therapy initiation

n = 28	At presentation	At corticosteroid initiation
Median age, y (range)	4 (1-16)	
Male sex, n (%)	20 (71)	
White blood cells, thou/μL, median (range)	5.9 (2.1-18.2)	6.2 (1.3-12.3)
Absolute lymphocytes, thou/μL, median (range)	2394 (112-12 194)	1211 (140-8118)
Hemoglobin, g/dL, median (range)	11.8 (7.3-16.5)	10.8 (6-13.6)
Platelets, thou/μL, median (range)	198 (6-594)	188 (26-736)
ALT, IU/L, median (range)	2181 (169-8402)	1517 (172-8402)
Total bilirubin, mg/dL, median (range)	11.4 (3.9-23.9)	16.6 (5.3-28.2)
INR, median (range)	1.6 (1.2-7)	2.3 (1.4-6.5)
Ammonia, μMol/L, median (range)	42 (9-109)	68 (10-151)
Hepatic encephalopathy stage 2-4, n (%)	3 (11)	7 (25)

with IND-PALF were a median of 4 years of age (range 1-16) and predominantly male (71%, n = 20); most (71%, n = 20) had a negative serum acetaminophen level recorded, and none had a history of acute ingestion. Eight patients with IND-PALF received therapeutic doses of acetaminophen intermittently over several days leading up to their ALF presentation, but none expressed the phenotype suggesting chronic acetaminophen toxicity.[17] The majority of patients with IND-PALF had negative testing for hepatitis A virus (96%, n = 27), hepatitis B virus (96%, n = 27), Epstein Barr virus (100%), and herpes simplex virus (96%, n = 27). In addition, a subset of patients had negative testing for cytomegalovirus (75%, n = 21), adenovirus (64%, n = 18), enterovirus (43%, n = 12), parvovirus B19 (43%, n = 12), and human herpes virus (HHV)-6 (18%, n = 5). Two patients had positive HHV-6 PCR testing thought to represent viral reactivation. No patients had positive testing for what was believed to be a causative virus. Regarding evaluation for AIH, 24 patients (86%) had negative ANA titers, 3 patients had low positive ANA titers ≤1:80, and 1 patient had a positive titer of 1:320; however, these patients had no other clinical evidence to suggest a diagnosis of AIH. One patient had low positive SMA titer of 1:80 but similarly no other evidence of AIH and the remainder of patients were SMA titer negative (96%, n = 27). All patients had negative LKM auto-antibody titers. All patients ≥4 years of age had negative screening for Wilson disease, and all patients ≤2 years of age had negative screening for metabolic disorders. **Table I** lists patient demographics and laboratory values on admission and at time of corticosteroid therapy. Seventeen (61%) patients had a liver biopsy performed prior to initiation of corticosteroid therapy, notable for acute hepatitis with portal and lobular inflammation, hepatocellular injury with variable degrees of collapse and necrosis, and no significant fibrosis.

Median age for the 6 patients with aplastic anemia with acute hepatitis was 9.5 years (range 1-12) and 83% (n = 5) were male. All 6 patients with aplastic anemia with acute hepatitis had a negative medication and supplement use history taken and no history of chronic acetaminophen ingestion. All patients had negative testing for hepatitis A, hepatitis B, and Epstein Barr viruses, with 4 patients (67%) also having negative testing for herpes simplex virus. In addition, a subset of patients had negative testing for cytomegalovirus (50%, n = 3), parvovirus B19 (50%, n = 3), adenovirus (33%, n = 2), HHV-6 (33%, n = 2), and enterovirus (17%, n = 1). No patients had positive testing for what was believed to be a causative virus. Regarding evaluation for AIH, all patients had negative ANA, SMA, and LKM titers. All patients ≥4 years of age had negative screening for Wilson disease, and all patients ≤2 years of age had negative screening for metabolic disorders. Most patients (n = 5) were admitted to the hospital, for a median of 7 days (range 3-15), and 1 patient was treated as an outpatient. On presentation median ALT was 2345 U/L (range 862-2612), total bilirubin 12.9 mg/dL (range 11.2-28), and INR 1.2 (range 1-1.5). Patient demographics and laboratory values at presentation and at time of corticosteroid therapy initiation are listed in **Table II**. All 6 patients had liver and bone marrow biopsies performed prior to initiation of corticosteroid therapy.

Table II. Aplastic anemia with acute hepatitis patient demographics and laboratory values at presentation and at time of corticosteroid therapy initiation

n = 6	At presentation	At corticosteroid initiation
Median age, y (range)	9.5 (1-12)	
Male sex, n (%)	5 (83)	
White blood cells, thou/μL, median (range)	2.6 (0.6-5.6)	1.7 (0.4-5.4)
Absolute lymphocytes, thou/μL, median (range)	480 (168-2240)	376 (101-1510)
Hemoglobin, g/dL, median (range)	13.4 (8.1-14.3)	11.8 (8.1-14.1)
Platelets, thou/μL, median (range)	168 (6-372)	119 (6-345)
ALT, IU/L, median (range)	2345 (862-2612)	2321 (561-2514)
Total bilirubin, mg/dL, median (range)	12.9 (11.2-28)	18.3 (7.7-25.6)
INR, median (range)	1.2 (1-1.5)	1.4 (1.1-1.7)

Table III. Laboratory values at 21 days postcorticosteroid therapy initiation and time to normalization for patients with IND-PALF and aplastic anemia with acute hepatitis who recovered with their native liver

	IND-PALF (n = 12)	Aplastic anemia with acute hepatitis (n = 6)
21 d postcorticosteroid initiation		
White blood cells, thou/μL, median (range)	7.1 (2.7-16.4)	2.5 (0.1-6.5)
Absolute lymphocytes, thou/μL, median (range)	2200 (110-5130)	1069 (114-2750)
Hemoglobin, g/dL, median (range)	10.5 (8.2-13)	10.2 (6.3-13.3)
Platelets, thou/μL, median (range)	352 (11-711)	36 (6-97)
ALT, IU/L, median (range)	328 (38-2885)	411 (38-1371)
Total bilirubin, mg/dL, median (range)	2.9 (1.3-12.5)	1.6 (0.5-6.3)
INR, median (range)	1 (0.9-1.9)	1.1 (0.9-1.1)
Median d to normal laboratory values (range)		
ALT	88 (18-205)	61 (20-180)
Total bilirubin	60 (21-84)	37 (24-90)
INR ≤1.2	12 (1-240)	3 (1-9)

Liver biopsy results were notable for acute hepatitis with portal and lobular inflammation, and bone marrow biopsy results revealed hypocellular marrow with no evidence of dysplasia.

The median duration of illness prior to initiation of corticosteroid therapy in patients with IND-PALF was 2 weeks (range 0-8); 20 were treated with a range of 0.5-4 mg/kg/day of intravenous methylprednisolone, and 8 patients received bolus doses of 10 mg/kg/day for several days followed by a taper. At the time of steroid initiation, 7 patients (25%) had evidence of stage 2-4 hepatic encephalopathy, and 15 patients (54%) reached a maximum of stage 2-4 hepatic encephalopathy during their admission. By 21-days postcorticosteroid therapy initiation 14 patients (50%) underwent liver transplantation, 13 patients (46%) were alive with their native liver and 1 patient (4%) died. By 90 days, postcorticosteroid initiation 1 additional patient underwent liver transplantation and 12 (43%) had recovered. Eight patients with IND-PALF (29%) developed aplastic anemia, diagnosed by bone marrow biopsy, of whom 2 underwent liver transplantation and their aplastic anemia resolved and 6 recovered with their native liver. Among those whose liver recovered, 4 had progression of their aplastic anemia requiring either additional immunosuppressive therapy (n = 2) or stem cell transplantation (n = 2). Bone marrow biopsy results were available for 7 of the 8 patients with aplastic anemia and notable for hypocellular marrow with no evidence of dysplasia. There was 1 serious infection within 90 days postcorticosteroid initiation, a fungal tracheitis (tracheal aspirate positive for *Candida glabrata*) in the patient who died during their ALF admission.

The 16 patients with IND-PALF who underwent liver transplantation or died had a median duration of hospital admission of 11 days (range 3-57) prior to reaching those end points. Median duration of corticosteroid therapy prior to death or liver transplantation was 5 days (range 1-37); 11 (69%) patients received at least 4 days of corticosteroid therapy before liver transplantation or death (median 7 days, range 4-37), and 5 patients (31%) underwent liver transplantation within 72 hours of initiating corticosteroid therapy. Patients who died or underwent liver transplantation were more likely to reach stage 2-4 hepatic encephalopathy during admission (n = 15, 94%), with 5 patients progressing to stage 4 coma, compared with no patients who recovered developing stage 2-4 hepatic encephalopathy. The 12 patients with IND-PALF who recovered with their native liver had a median total duration of hospital admission of 14 days (range 7-42) and received a median of 139 days (range 19-749) of corticosteroid therapy. ALT level decreased to <500 U/L by a median of 30 days (range 15-89) postcorticosteroid initiation. Table III lists 21-day postcorticosteroid laboratory values and interval to normal for patients who recovered with their native liver.

The median duration of illness prior to corticosteroid initiation for patients with aplastic anemia with acute hepatitis was 3 weeks (range 2-8). All 6 patients received 1-2 mg/kg/day of methylprednisolone, with 5 starting with intravenous therapy and 1 with oral therapy, for a median of 100 days (range 63-183). At 21- and 90-days postcorticosteroid initiation, all patients with aplastic anemia with acute hepatitis had recovered with their native liver, however, 4 had progression of their aplastic anemia requiring either additional immunosuppressive therapy (n = 1) or stem cell transplantation (n = 3). ALT level decreased to <500 U/L by a median of 32 days (range 1-100) postcorticosteroid initiation. Table III lists 21-day postcorticosteroid laboratory values and interval to normal for aplastic anemia with acute hepatitis patients. Two patients developed a serious infection within 90 days postcorticosteroid initiation, 1 with *Clostridium septicum* sepsis and neutropenic colitis, and the other with *Staphylococcus aureus* sepsis and invasive fungal pneumonia (*Dematiaceus fungi*). Both patients were being treated with low-dose corticosteroids (<1 mg/kg/day) and were neutropenic with absolute neutrophils <200 thou/μL at the time of the infections.

Additional data regarding serum biomarkers of immune activation status were available for a subset of patients with IND-PALF and aplastic anemia with acute hepatitis. Serum sIL-2R level was elevated for age in all patients in which it was measured (16 IND-PALF and 5 aplastic anemia with acute hepatitis) with median levels of 4574 pg/mL (range 1677-14 285) and 3963 pg/mL (range 3416-11 659), respectively.

In 7 (44%) of the patients with IND-PALF, the sIL-2R level was significantly elevated at >5000 pg/mL, of whom 5 recovered with their native liver and 2 underwent liver transplantation. Natural killer cell function was decreased or absent in 11 (85%) of the 13 patients with IND-PALF and 2 (67%) of the 3 patients with aplastic anemia with acute hepatitis in which it was measured. T- and B-cell quantitation by flow cytometry was performed on peripheral blood from 11 patients with IND-PALF and 5 patients with aplastic anemia with acute hepatitis, and the ratio of CD4 to CD8 T-cells was decreased (≤1.0) in 3 of the patients with IND-PALF (27%), 2 of whom developed aplastic anemia, and in 4 (80%) of the patients with aplastic anemia with acute hepatitis.

Discussion

This multicenter study examined the clinical characteristics and outcomes of patients with IND-PALF treated with corticosteroids for immune dysregulation. The outcomes are similar to those reported in the initial publication from the PALFSG cohort, which included 348 patients, 169 with indeterminate diagnosis.[14] By 21 days poststudy entry, 42% of the indeterminate group had undergone liver transplantation, 43% were alive with their native liver, and 15% had died. However, comparisons between these groups should be limited as our cohort represents a selected subset of patients with IND-PALF with features of immune dysregulation rather than of the PALFSG indeterminate cohort as a whole. The percentage of patients who died was lower in our study compared with the historical PALFSG cohort, which may be reflective of both improvement in supportive care in addition to the corticosteroid therapy. However, the percentage of patients who underwent liver transplantation was similar in both groups. Notably, 5 patients in our study who were transplanted received ≤72 hours of corticosteroid therapy prior to their surgery, suggesting that the complete effect of steroids may not have been realized. This underscores the complexity of the role of transplant in the setting of acute liver failure where, once listed, the decision to refuse an acceptable organ must be weighed against the potential for recovery and the chances that another suitable organ becomes available. A publication from the PALFSG includes an expanded cohort of 986 patients with PALF, of whom 437 (44%) had an indeterminate diagnosis, with similar 21-day outcomes.[18] In another study comparing older PALFSG cohorts (1999-2010, n = 515) with the most recent cohort (2012-2014, n = 143), the percentage of patients diagnosed as indeterminate decreased (48% vs 31%), and the overall cumulative incidence rate for liver transplantation at 21 days decreased with no significant change in incidence of death.[16] As all 4 centers included in this study are part of the PALFSG, one can assume that a subset of patients included in the more contemporary PALFSG cohort were treated with corticosteroids, but PALFSG data collection did not specifically track this therapy beyond the first week of care.

Corticosteroid therapy has been studied in adult patients with ALF and the majority of studies have failed to show any treatment survival benefit.[19-22] This includes a randomized clinical trial of 40 patients with ALF, 26 treated with corticosteroids and 14 with standard of care, in which there was no difference in survival between the 2 groups.[19] The Acute Hepatic Failure Study Group conducted a multicenter double-blinded study of daily hydrocortisone therapy (n = 44) compared with placebo (n = 18) in patients with ALF and found no therapeutic benefit.[21] A retrospective review of the use of corticosteroids in 361 patients in the Acute Liver Failure Study Group who had liver failure due to possible immune-mediated pathogenesis (autoimmune, indeterminate, and drug-induced) found that treatment was not associated with increased overall survival (61% vs 66%), or increased survival in any of the diagnostic groups.[22] In a subgroup analysis, patients who received corticosteroids and had ALT levels in the higher 50% of values had significantly improved survival with native liver, suggesting that higher ALT levels may be a marker of a more inflammatory and corticosteroid-responsive process.[22] Publications that have reported a benefit of corticosteroid therapy in adult patients with ALF include a retrospective single-center review in which 34 patients with ALF treated with corticosteroid therapy had a significantly increased rate of survival with native liver compared with 39 patients who did not receive corticosteroids (29.4% vs 5.1%, $P = .013$).[23] Improved rates of survival were seen in patients treated with corticosteroids who had higher ALT levels and who received early (≤2 weeks) compared with late (>2 weeks) steroid therapy.[23]

In the pediatric population, ALF is more prevalent in young children, who may mount different innate and adaptive immune responses compared with adults. Furthermore, children may be susceptible to a form of immune-dysregulation that is not seen in older patients, which is supported by the fact that in the adult cohort with ALF, only 17% of patients are classified as indeterminate.[24] Our study clearly reflects that there is a growing trend at pediatric liver transplant centers over the past decade to treat patients with IND-PALF with immunosuppressive therapy, however, the risks and benefits of this therapy have not been rigorously tested. Glucocorticoids produce broad anti-inflammatory effects including limiting T-cell activation, and, therefore, it is reasonable to hypothesize that they may benefit patients with IND-PALF who have evidence of immune activation. In children, the only published experience treating indeterminate ALF with corticosteroids is a case series by McKenzie et al describing 7 patients with indeterminate ALF and 2 patients with indeterminate acute hepatitis thought to have immune-dysregulation who were treated with intravenous immunoglobulin and methylprednisolone.[7] All patients with ALF had a decrease in ALT and total bilirubin, and 5 recovered with their native liver and 3 underwent liver transplantation. Liver biopsy specimens from indeterminate patients with PALF are characterized by a dense CD8+ T-cell inflammatory infiltrate, which clearly differentiates them from known diagnosis PALF cases.[6] This finding further supports the hypothesis that the liver injury in many patients with IND-PALF is immune-mediated and may respond to immunosuppressive therapy.

There are still significant gaps in the understanding of the progression of idiopathic aplastic anemia, but it is thought to be an immune mediated disease involving CD8+ T-cell injury to hematopoietic stem cells. The disorder is characterized by high serum levels of interferon gamma, and first line therapy includes treatment with immunosuppressive agents.[25] It is not uncommon for children with aplastic anemia to present with concurrent acute hepatitis, and multiple studies have noted that treatment of the aplastic anemia often results in improvement in liver enzymes.[8,10,12,13] Patel et al described 7 children with indeterminate acute hepatitis and aplastic anemia with a T-cell predominant infiltrate on liver biopsy, 3 of whom were treated with immunosuppressive therapy (including antithymocyte globulin, cyclosporine A, and prednisone) with subsequent improvement in symptoms, liver enzymes, and hepatic inflammation.[9] A similar case series by Taylor et al describes 2 patients with acute hepatitis and aplastic anemia who were treated with antithymocyte globulin, cyclosporine, and solumedrol with complete recovery.[12] These studies suggest immunosuppressive therapies may improve both liver and bone marrow function in these patients, supporting a common underlying pathophysiologic mechanism. In our series, a significant percentage of patients who developed aplastic anemia recovered with their native liver, suggesting corticosteroids may be particularly beneficial for treating the acute liver injury in this group. However, corticosteroids may not be sufficient to rescue the bone marrow, as many patients went on to require additional immunosuppressive therapy or stem cell transplantation. Early clinical markers that may be used to predict which patients with IND-PALF will develop aplastic anemia include peripheral blood cytopenias and a decreased CD4 to CD8 T-cell ratio on flow cytometry.[26] In addition, it is important to consider that these patients may be profoundly neutropenic and at increased risk of infection.

Limitations of our study include that analyses were conducted retrospectively and at the time of treatment decisions there were no standardized diagnostic criteria for the immune dysregulation phenotype. Treatment with corticosteroids was at the discretion of the attending physician, was not randomized, and was not standardized with regards to timing, dose, or duration. Specifically, patients received a wide range of corticosteroid dosing regimens, which may have influenced treatment responses and outcomes. The workup of indeterminate cases was reviewed, and most patients had complete age-specific diagnostic testing, however, it is possible some cases had a known diagnosis that was not identified.

In summary, we report 34 patients (28 with IND-PALF and 6 with aplastic anemia with acute hepatitis) who were treated with corticosteroids, primarily in the setting of immune-activation. Infectious complications were rare. Many patients improved, but survival with native liver may not be different from historical reports. Empiric use of corticosteroids in the future may be better targeted to those patients with IND-PALF with the strongest evidence of an immune-dysregulation phenotype (including evidence of T-cell activation such as elevated sIL-2R levels, and liver biopsy with predominant CD8+ T-cell inflammation). However, the risks and benefits of specific immunosuppressive therapy for IND-PALF need to be tested in a randomized controlled clinical trial before any treatment is adopted broadly. ■

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50 Years Ago in *The Journal of Pediatrics*

Malnutrition and Brain Development

Winick M. J Pediatr 1969;74:667-79

In this seminal review, Myron Winick cited animal experiments and human studies on childhood nutritional deprivation, endeavoring to answer the question "What is the functional result of having survived malnutrition as an infant?" He concluded that there was sufficient evidence linking early childhood malnutrition to permanent neurodevelopmental deficits (ie, reductions in brain weight and head circumference, cellular proliferation, myelination, and diminished cognition) to shift the bulk of nutrition resources toward the critical period before birth and during early postnatal life. He was a pioneer in determining that these deficits have an intergenerational component, and he anticipated the importance of acknowledging and measuring the social determinants of disease.

Since the publication of this review, 50 years of mounting evidence has solidified "the first 1000 days" as the prime target for nutritional interventions. Research on the topic now includes the roles of individual nutrients, systemic inflammation, and breastfeeding on neurodevelopmental outcomes. However, our understanding remains plagued by the same challenges cited by Winick, including the difficulty in establishing causal relationships and the lack of consensus and standardization regarding assessment tools. As a result, growth attainment measures, including linear growth[1] and head circumference, remain frequently utilized surrogates for cognitive development, highlighting the limits of our advancement. Notable improvements in the field include more detailed neuroimaging, techniques to measure neurophysiologic outcomes, and new development assessment tools.

Conservatively, an estimated >200 million children fail to reach their potential in cognitive development, resulting in reductions in educational achievement, economic productivity, and earnings.[2,3] Going forward, we must insist on incorporating these outcomes, alongside growth attainment, in the design and interpretation of child nutrition and cognitition research.

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