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Early increase in body mass index and cardiometabolic risk in adolescence

To the Editor:

In an assessment of the influence of the weight gain trajectory from birth to 14 years old, Barraclough et al found that an early increase in body mass index (BMI) above the 90th percentile before 3 years of age resulted in an unfavorable cardiometabolic risk profile in adolescence, compared with children with a late increase in BMI.[1] This finding is important because early identification of children with likely future cardiometabolic risks is essential for promoting cardiovascular health in early childhood.[2]

We would like to add our view on the relationship between the early BMI pattern and cardiometabolic risk. Early excess BMI before 3 years of age is important in relation to future cardiometabolic risk, but it is not necessary for the child to be overweight or obese at the start of the BMI rise.[1,3] We have found that a BMI increase from age 1.5 to 3.0 years, even if BMI is in the normal range just before the increase, is related to a greater increase in Homeostatic Model Assessment of Insulin Resistance per BMI increase at age 12 years compared with a stable or decreased BMI from 1.5 to 3.0 years of age.[4-6] These data were obtained from 1.5- and 3.0-year-old checkups, including weight and height measurements, as defined by the Ministry of Health, Labour and Welfare in Japan. This finding suggests that children with a BMI increase before age 3 years, a period normally characterized by decreased BMI, are more prone to developing insulin resistance in adolescence. Furthermore, another analysis of longitudinal growth data indicated that BMI rebound (adiposity rebound) earlier than approximately 3 years of age with lower pre-rebound BMI leads to greater risk of childhood obesity.[7]

These results suggest that an early increase in BMI before age 3 years is important, even if the absolute BMI is low, because this BMI pattern is closely related to cardiometabolic risk in adolescence.

Osamu Arisaka, MD, PhD
Go Ichikawa, MD, PhD
Department of Pediatrics
Nasu Red Cross Hospital
Ohtawara, Tochigi-ken, Japan

Satomi Koyama, MD, PhD
Department of Pediatrics
Dokkyo Medical University School of Medicine
Mibu, Tochigi-ken, Japan

Toshimi Sairenchi, PhD
Department of Public Health
Dokkyo Medical University School of Medicine
Mibu, Tochigi-ken, Japan

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Immunosuppressive therapy for indeterminate acute hepatitis or pediatric acute liver failure

To the Editor:

Chapin et al reported the use of corticosteroid treatment for children with indeterminate pediatric acute liver failure (PALF) and children with aplastic anemia and acute hepatitis.[1] This allows us to draw attention to our reported cohort of 38 children with a liver disease of indeterminate etiology, in most cases presenting with acute hepatitis (n = 14) or with PALF (n = 15).[2] This condition was tentatively called "seronegative autoimmune hepatitis" because of the liver histology, the prompt response to immunosuppressive therapy used in typical autoimmune hepatitis[3,4] (prednisone alone or with azathioprine or cyclosporine), and the lack of specific autoantibodies. These features, combined with the lack of evidence of known causes of acute and chronic liver diseases, suggested immune dysregulation and activation. In particular, 10 children presented with acute hepatitis (PALF in 9) and aplastic anemia: 8 of these displayed lymphocytopenia ($\leq$800/mm^3) at diagnosis of hepatitis with a low proportion of CD4+ T lymphocytes. Liver transplantation was performed in 1 patient due to liver failure. In the other 9 subjects, immunosuppressive treatment was associated with normalization of liver function within 2 months without recurrence of the liver disease. The treatment of aplastic

anemia was successful in all and consisted of cyclosporine with or without antilymphocyte globulin and of an human leukocyte antigen−identical bone marrow transplantation.

Moreover, of the other 28 children, 19 presented with acute hepatitis, including 13 with abnormal prothrombin time (<70%) and 6 with PALF. All responded to immunosuppressive therapy and were alive at the time of writing. Lymphopenia was found at onset of hepatitis in 5 children. Our data agree with the conclusion of Chapin et al that evidence of immune dysregulation including lymphopenia should be searched in patients with indeterminate acute hepatitis or PALF to better target the use of immunosuppressive therapy and avoid liver transplantation.

Giuseppe Maggiore, MD
Department of Medical Sciences
Section of Pediatrics
University of Ferrara and
Pediatric Hepatology and Liver Transplantation
ISMETT-University of Pittsburgh Medical Center Italy
Palermo, Italy

Emmanuel Jacquemin, MD, PhD
Olivier Bernard, MD, PhD
Pediatric Hepatology and Pediatric
Liver Transplantation Unit
National Reference Center for rare pediatric
liver diseases and Filfoie
Hôpital Bicêtre
Assistance Publique-Hôpitaux de Paris
Le Kremlin-Bicêtre, France
Faculty of Medicine Paris - Sud
University Paris - Sud / Paris – Saclay and
INSERM UMR-S1174 and Hepatinov
Orsay, France

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Reply

To the Editor:

We thank Maggiore et al for their thoughtful commentary regarding our article discussing corticosteroid therapy for children with indeterminate acute hepatitis and acute liver failure. We have read with interest their article describing the spectrum of disorders seen in children with what they labeled "seronegative autoimmune hepatitis."[1] This descriptive term was used for convenience, and in their letter the authors state that the children with hepatitis, normal IgG levels, and blood cytopenia or aplastic anemia had features more consistent with immune activation and dysregulation. We agree with this impression and propose that those patients had liver disease secondary to activated CD8 T-cell hepatitis (formerly indeterminate acute hepatitis or indeterminate acute liver failure), which is distinct from autoimmune hepatitis.

Differentiating between children with acute onset of seronegative autoimmune hepatitis and activated CD8 T-cell hepatitis can be challenging and may require observation of disease progression and response to therapy over time. Patients with activated CD8 T-cell hepatitis present acutely and may have coincident peripheral blood cytopenia or aplastic anemia. Signs and symptoms of chronic liver disease are absent, autoantibodies are typically negative, and the serum gamma globulin level is usually normal. Liver histology is characterized by lobular and portal lymphocytic inflammation, predominantly with CD8+ T cells,[2] without interface hepatitis or prevalence of plasma cells. The disease does not recur either postrecovery with native liver or postliver transplantation and does not require ongoing immunosuppressive therapy. As our case series demonstrates, outcomes for these patients when treated with corticosteroids are variable.[3] In our cohort, 21-day postcorticosteroid treatment outcomes for children with acute liver failure were similar to historical controls, with 50% undergoing liver transplantation. It remains unknown whether treatment with immunosuppressive therapy might alter the disease trajectory and should be studied in the context of a prospective randomized clinical trial. Case series and case reports describe improvement in hepatitis associated with aplastic anemia when treated with immunosuppressive therapy,[4-6] and all of the children in our study recovered with their native liver. In our experience, this milder form of liver injury also may resolve without any intervention. However, the aplastic anemia is frequently more severe, and many patients undergo bone marrow transplantation.[7] These findings agree with those of Maggiore et al, who reported that all 16 children (groups 3 and 4) with hepatitis, normal IgG, and blood cytopenia or aplastic anemia recovered from their acute liver injury with immunosuppressive therapy and did not recur when treatment was discontinued.[1] As noted, lymphopenia may be an important clinical indicator of patients with activated CD8 T-cell hepatitis who later develop aplastic anemia. We have also found a decrease in CD4 to CD8 T-cell ratio on flow cytometry to be a marker of this subpopulation.[8,9]

Catherine A. Chapin, MD
Estella M. Alonso, MD
Northwestern University Feinberg School of Medicine and
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois

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