Nonalcoholic Fatty Liver Disease in Italian Children with Down Syndrome: Prevalence and Correlation with Obesity-Related Features

Diletta Valentini, MD[1,*], Anna Alisi, PhD[2,*], Chiara di Camillo, MD[1], Maria Rita Sartorelli, MD[3], Annalisa Crudele, PhD[2], Andrea Bartuli, MD[4], Valerio Nobili, MD[3], and Alberto Villani, MD[1]

Objective To assess the prevalence of overweight/obesity in a cohort of Italian children with Down syndrome (DS) and to investigate the correlation of both obesity and DS with nonalcoholic fatty liver disease (NAFLD).

Study design We enrolled 280 children with DS (age range 5-18 years), who were referred to the DS outpatient clinic of the Bambino Gesù Children's Hospital in Rome. For all children, we collected the clinical history and measured anthropometric variables. Eighty-four of 280 children with DS were selected to undergo liver ultrasound scanning to evaluate the presence of NAFLD.

Results Italian children with DS exhibited a prevalence of 19.64% for overweight and 12.14% for obesity. The prevalence of NAFLD in nonobese (45%) and overweight/obese (82%) children with DS is greater than in the European pediatric nonobese (5.7%) or obese population (33%). Moreover, the severity of liver brightness on ultrasound scan correlated positively with body mass index, triglycerides, low-density lipoprotein-cholesterol, and leptin levels and negatively with adiponectin.

Conclusions We demonstrated that, independently from the obese phenotype, children with DS display a greater risk to develop NAFLD than the general pediatric population. *(J Pediatr 2017;189:92-7).*

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Down syndrome (DS) is the most common chromosomal disorder, with a prevalence ranging from 6.1 to 13.1 per 10 000 people.[1] Although improvements in medical care have led to an increased life expectancy, efforts are still needed to implement healthcare services for individuals affected by this condition.[2] Children with DS exhibit a high prevalence of various comorbid medical conditions.[3] Among the many conditions associated with DS in the pediatric setting, obesity is one of the most common. Childhood obesity is following the widespread epidemic of adult obesity.[4] In fact, it is estimated that at least 155 million children worldwide are overweight or obese.[5,6] The prevalence of overweight and obesity in children with DS is greater than general pediatric population, ranging from 23% to 70%.[7] Aburawi et al[8] demonstrated that rates of overweight and obesity increase after 2 years of age in children with DS.

Risk factors of overweight/obesity in the general pediatric population include increased unfavorable dietary patterns, lower levels of physical activity, and comorbidities such as thyroid disorders and severe congenital heart diseases.[9] The same factors also could influence body weight in children with DS.[10-12] The few available studies on these subjects do not yet provide convincing evidence for any specific relationship. In addition, several studies reported that high levels of leptin, a well-known adipocytokine, could be an additional determinant of obesity in children with DS.[13-15]

Similarly to children without DS, obesity in children with DS is associated with several diseases including obstructive sleep apnea,[16] orthopedic and gait abnormalities,[17] and metabolic syndrome features such as dyslipidemia and hyperinsulinemia.[14,18,19]

Epidemiologic studies found together with the increase in pediatric obesity, an increased prevalence of nonalcoholic fatty liver disease (NAFLD).[20] NAFLD currently is considered the most frequent chronic liver disease worldwide.[20,21] Genetic

AST	Aspartate aminotransferase
BMI	Body mass index
DS	Down syndrome
HDL	High-density lipoprotein
HOMA-IR	Homeostasis model assessment-insulin resistance
IL-6	Interleukin-6
LDL	Low-density lipoprotein
NAFLD	Nonalcoholic fatty liver disease
PNFI	Pediatric NAFLD fibrosis index
TNF-α	Tumor necrosis factor-α
WC	Waist circumference

From the [1]Pediatric and Infectious Disease Unit; [2]Liver Research Unit; [3]Hepato-Metabolic Disease Unit; and [4]Rare Diseases and Medical Genetic Unit, Bambino Gesù Children's Hospital, Institute for Research and Health Care (IRCCS), Rome, Italy

*Contributed equally.

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susceptibility and inappropriate lifestyle (ie, over-/malnutrition and physical inactivity) are the main risk factors for NAFLD both in children and adults.[22,23] However, the pathogenesis is multifactorial; a growing body of evidence has demonstrated that, among different pathogenic factors, adipocytokines may play pivotal roles in the development and/or progression of NAFLD.[24] Among the adipocytokines involved in NAFLD pathogenesis are those mainly involved in energy balance control, lipid and glucose metabolism, insulin sensitivity, blood pressure, and angiogenesis (adiponectin, leptin, and resistin) as well as those that trigger inflammation (proinflammatory cytokines, including interleukin-6 [IL-6] and tumor necrosis factor-α [TNF-α]).[24] Therefore, in this study, we assessed the prevalence of overweight/obesity in a cohort of Italian children with DS and the possible correlation with NAFLD diagnosed by an ultrasound scan of the liver.

Methods

Children with DS (n = 280; age range 5-18 years) participated in this study. The children were recruited from the DS outpatient clinic of the Bambino Gesù Children's Hospital in Rome from December 2014 until March 2016. Inclusion criteria were diagnosis of DS proven by chromosome analysis; age between 5 and 18 years; and body mass index (BMI) ≥ third percentile for age and sex.

For all children, we collected the clinical history with particular focus on lifestyles (diet and exercise) and the presence of comorbidities. Anthropometric variables (weight, height, BMI) also were measured and collected.

A subpopulation of 84 subjects of the 280 initially enrolled was selected because they had no endocrinologic disorders, hemodynamically significant congenital heart diseases, celiac disease, neoplastic conditions, history of intestinal anomalies requiring bowel resection, and/or ongoing medical intervention and concurrent infections. Second, these subjects underwent further investigations that included anthropometrics (weight, waist circumference [WC], and BMI); ultrasound scan of the liver; and biochemical variables and adipocytokines. The patients also were checked simultaneously for hepatic viral infections (hepatitis A, B, C, D, and E viruses; cytomegalovirus; and Epstein-Barr virus), alcohol consumption, history of parenteral nutrition, and use of drugs known to induce steatosis (eg, valproate, amiodarone, or glucocorticoids) or to affect body weight and carbohydrate metabolism, autoimmune liver disease, metabolic liver disease, Wilson disease, and 1-alpha-antitrypsin-associated liver disease.

Written informed consent was obtained from parents. The study was approved by the Ethics Committee of the Bambino Gesù Children's Hospital and was conducted according to the principles of the Declaration of Helsinki.

Weight was measured without clothing and/or diapers on an electronic digital scale. Standing height was measured via a wall-mounted stadiometer. BMI, defined as weight in kilograms divided by height in meters squared, was calculated. Because BMI varies with age and differs by sex, BMI percentile was calculated with standard growth charts of the World Health Organization, according to the American Academy of Pediatrics Statement for children with DS.[25] WC was measured, with the patient in a standing position, on the horizontal plan between the lowest portion of the rib cage and the iliac crest. Weight, height, and WC were measured by one physician only.

Blood sampling was performed at the time of NAFLD diagnosis after an overnight fast. Laboratory tests by automated commercial methods included analysis of alanine aminotransferase, aspartate aminotransferase (AST), and gamma-glutamyltransferase; total cholesterol; high-density lipoprotein (HDL)-cholesterol; low-density lipoprotein (LDL)-cholesterol; triglycerides; glucose; insulin; and uric acid.

The homeostasis model assessment-insulin resistance (HOMA-IR) was calculated to assess insulin sensitivity and beta-cell function.[26] HOMA-IR formula was fasting plasma insulin in mU/L × fasting plasma glucose in mmol/L/22.5.

An ultrasound scan of the liver was performed by an experienced radiologist, using an Acuson Sequoia C512 scanner equipped with a 15L8 transducer (Universal Diagnostic Solutions, Oceanside, California). Normal liver/absent steatosis was defined as having normal liver echo-texture; mild steatosis as slight and diffuse increase in fine parenchymal echoes with normal visualization of diaphragm and portal vein borders; moderate steatosis as moderate and diffuse increase in fine echoes with slightly impaired visualization of diaphragm and portal vein borders; and severe steatosis as fine echoes with poor or no visualization of diaphragm, portal vein borders, and posterior portion of the right lobe.[27] The circulating levels of adiponectin, leptin, TNF-α, and IL-6 were measured according to the manufacturer's recommendations by commercially available enzyme-linked immunoassay kits (BioVendor, Heidelberg, Germany).

Statistical Analyses

Statistical analysis was performed with the software packages GraphPad Prism 5.00 and GraphPad Instat 3.05 (GraphPad Software, Inc, San Diego, California). Data are shown as mean ± SD. Two-tailed P values <.05 were considered statistically significant. Multiple comparisons were made with the Spearman correlation. Linear regression analysis was used to study the relationship between the liver fat content and the other variables.

Results

The study population, consisting of 280 children with DS (age range 5-18 years), was screened for overweight/obesity. As reported in **Figure 1** (available at www.jpeds.com), we found 191 children with a normal weight (BMI 3-84th percentile), 55 overweight children (BMI 85-94th percentile), and 34 obese children (BMI ≥95th percentile). Therefore, our data showed, in Italian children with DS, a prevalence of 19.64% for overweight and of 12.14% for obesity.

As reported in **Figure 2** (available at www.jpeds.com), we selected 84 of 280 children to collect accurate anthropometric data and to analyze several biochemical and metabolic