

COMMENTARY**In memory of Valerio Nobili – Mr NASH****Angelo Pietrobelli^{1,2}  | Alberto Villani³**¹Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, Pediatric Clinic, University of Verona, Verona, Italy²Pennington Biomedical Research Center, Baton Rouge, Louisiana³Department of Pediatrics, Bambino Gesù Children's Hospital (IRCCS), Rome, Italy**Correspondence**

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Valerio Nobili built his career around his passion for caring for pediatric patients with nonalcoholic steatohepatitis (NASH) and understanding its pathophysiology so that better treatment and prevention options could be developed. He was first and foremost a pediatrician, and cared deeply for the children and families that he treated. Many young patients called him “the doctor with big arms”—he always offered big hugs to them. He was a leader in his field with enormous energy that was brought to an end far too soon. Valerio was biking when the heart stopped on March 2019—he was only 53. He published 384 papers in outstanding medical journals; he was head of the Metabolic and Autoimmunity Liver Unit, Pediatric Department of Pediatrics, Bambino Gesù Children's Hospital and Associate Professor at University “La Sapienza,” Rome.

Looking at his career, two of the articles always cited by Valerio were published in 2008. The first one¹ focused on pediatric Non Alcoholic Fatty Liver Disease (NAFLD), and defined the disease as under diagnosed and under treated despite a prevalence that was growing exponentially. Valerio and his colleagues pointed out that

environmental background for the development of NAFLD may be established early in life and associated with abdominal adiposity, insulin resistance and features of the metabolic syndrome. In this paper, Valerio emphasized how excessive nutrients cannot be stored in the adipose tissue and overflow elsewhere, mainly to the muscle mass and liver.¹ In the same year, Valerio and his group looked at treatment of NAFLD in children and adolescents and determined the efficacy of lifestyle intervention with or without antioxidant therapy.² The authors found that lifestyle intervention with diet and increased physical activity induces weight loss and is associated with significant improvement in liver histology.² In 2010, Valerio and his group published an article³ where genetic variability characterized by polymorphism in genes involved in the development and progression of the disease to NASH was analyzed. It is important to underline NASH that is considered the progressive form of NAFLD characterized by necro-inflammatory changes, ballooning degeneration, and/or fibrosis, can progress to liver failure and hepato-carcinoma.

In 2011, together with the Italian Hobbit Network,⁴ he presented data suggesting that nutrition in early life could be considered as an important risk factor for non-communicable diseases of adulthood. Different epigenetic mechanisms involved and influenced the susceptibility to develop metabolic diseases in adulthood were discussed starting either from maternal under- and over-nutrition and its interaction with genes controlling lipid and carbohydrate metabolism, thus inducing alteration on different organs (ie, liver).⁴ This article was pioneering in pointing out the hypothesis that the biological function of probiotics could be the result of epigenetic modifications that explain the capability to prevent the development of chronic immune-mediated diseases.⁴ One year later together with the same group, Valerio presented data that liver may represent one of the candidate organs targeted by programming, undergoing structural, functional, and epigenetic changes following exposure to an unfavorable intra-uterine environment and contributing to increased cardio-metabolic risk.⁵ In the same year, Valerio published an article where, once again,

he discussed the key role exerted by liver fat deposition in the development of the Metabolic Syndrome, in a process that was established in early life.⁶

In 2016, Valerio and his group together with Dr Jeffrey Schwimmer from UC San Diego discussed NAFLD and the serious health implications not only for adults, but also for children.⁷ In fact, diagnosis and treatment of pediatric NAFLD represent a major challenge for physicians. In order to address this challenge, hepatologists, pediatricians, and researchers must collaborate to gain insight into mechanisms of NAFLD development and progression in children. The dissection of NAFLD patho-physiology, in both children and adults, is needed in order to develop tools to improve early detection and treatment of disease as soon as possible.⁷ Valerio was a global leader in bringing these issues to light.

The idea of having early indices of liver damage progression was fundamental in Valerio's line of research. Despite that fact that liver biopsy in pediatrics remains the most accurate diagnostic method providing data on the degree of hepatic histological changes, Valerio worked to identify other prognostic factors influencing progression of NAFLD in order to identify children for special monitoring program, preventive therapeutic strategies, and specific treatments.⁸

In September of 2019, Nature Reviews Endocrinology published a critical article which can be defined in hindsight as his "scientific will" as a researcher.⁹ Despite progress in understanding the complexity of NAFLD, the pathophysiological mechanisms involved in the onset and progression of liver damage remain unclear.⁹ The article provided an overview of current concepts and new scientific advancements in our understanding of the epidemiology, pathogenesis, diagnosis, and treatment of pediatric NAFLD. Once again Valerio and his group underlined a great necessity to identify reliable noninvasive biomarkers that enable the stratification of patients into those with mild and severe disease.⁹

On top of this research career, he was an extraordinary clinician with great diagnostic acumen and a unique teacher. He was a big inspiration for us and for many other that were aware of his huge contribution to research and clinical work. He had a giant presence that

exuded energy, passion and inspiration. He is very sadly missed. Ciao Valerio.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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