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Recurrent *fructoholic* liver disease after liver transplantation in a patient with Maple Syrup Urine Disease

Susana Catarina Borges Silva

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RECURRENT *FRUCTOHOLIC* LIVER DISEASE AFTER LIVER TRANSPLANTATION IN A PATIENT WITH MAPLE SYRUP URINE DISEASE

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Susana Catarina Borges Silva

Aluna do 6º ano profissionalizante de Mestrado Integrado em Medicina

Afiliação: Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Endereço: Rua de Jorge Viterbo Ferreira nº228, 4050-313 Porto

Endereço eletrónico: 597susana@gmail.com

Orientadora: Esmeralda Emília Gomes Martins

Assistente Hospitalar Graduada Sénior do Serviço de Pediatria - Centro Materno-Infantil do Norte

Professora Associada Convidada

Endereço eletrónico: esmeralda.martins@chporto.min-saude.pt

Coorientadora: Ermelinda Ramalho Santos Silva

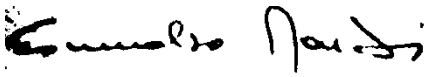
Assistente Hospitalar Graduada do Serviço de Pediatria - Centro Materno-Infantil do Norte

Professora Auxiliar Convidada

Endereço eletrónico: ermelinda.dca@chporto.min-saude.pt

Autora

Orientadora



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Dedicatória

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Resumo

A Leucinose (MSUD) é uma doença hereditária do metabolismo dos aminoácidos de cadeia ramificada, com clínica de predomínio neurológico, que se manifesta de forma clássica no período neonatal. O tratamento consiste na restrição dietética de aminoácidos de cadeia ramificada, calculada para promover o crescimento e desenvolvimento normais, e no tratamento de episódios de descompensação metabólica aguda. O transplante hepático é uma opção reservada para pacientes com controlo difícil. A utilização pouco rigorosa de uma dieta restrita em proteínas pode propiciar uma maior ingestão de lipídios e carboidratos, nomeadamente frutose, e ser responsável por uma lesão hepática semelhante à causada pelo consumo excessivo de álcool.

É relatado o caso de um adolescente do sexo masculino, diagnosticado no período neonatal com Leucinose, em que o não cumprimento da dieta restrita em aminoácidos de cadeia ramificada, a partir da idade escolar, levou a um mau controlo metabólico, com consequente deterioração da função cognitiva, e a um quadro de síndrome metabólica (obesidade, hipertrigliceridemia, hipertensão, resistência à insulina e doença do fígado gordo não alcoólico). Com o intuito de melhorar o controlo metabólico e de prevenir repercussões neurocognitivas adicionais, o doente foi submetido a transplante hepático (dador cadáver, jovem, enxerto sem esteatose). Pouco tempo depois, apresentou transaminases elevadas e esteatose na histologia do enxerto. Na anamnese aprofundada, a etiologia parecia estar relacionada com o consumo elevado de açúcar, especialmente, bebidas adoçadas com frutose.

A recorrência de esteatohepatite não-alcoólica após o transplante hepático já foi mencionada em adultos, mas não está bem documentada em idade pediátrica.

O principal objetivo deste trabalho é contribuir para o conhecimento da Doença do Fígado Gordo Não Alcoólico em idade pediátrica e destacar o impacto da obesidade e da dieta rica em frutose no desenvolvimento da patologia. O rápido desenvolvimento de esteatose no enxerto sugere que a desregulação metabólica é capaz de reproduzir a doença num órgão saudável e que apenas uma mudança sustentada na dieta pode prevenir a sua recorrência.

Abstract

Maple syrup urine disease (MSUD) is an inherited disorder of branched-chain amino acids (BCAA) metabolism, with predominantly neurological manifestations, which manifests in a classic form in the neonatal period. Treatment consists of BCAA dietary restriction, calculated to promote normal growth and development, and treatment of acute metabolic decompensation episodes. Liver transplant is an option reserved for patients difficult to manage. A non-rigorous use of a protein restrictive diet can lead to a greater intake of lipids and carbohydrates, namely fructose, which can be responsible for a liver injury, similar to that caused by excessive alcohol consumption.

It is reported the case of a male adolescent diagnosed in the neonatal period with MSUD in which the non-compliance with a BCAA restricted diet from the school-age led to poor metabolic control, with consequent deterioration of cognitive function, and a clinical condition known as metabolic syndrome (obesity, hypertriglyceridemia, hypertension, insulin resistance, and NAFLD). To improve metabolic control and prevent additional neurocognitive repercussions, the patient underwent liver transplantation (young cadaveric donor, graft without steatosis). Shortly afterward, he once more showed elevated transaminases and steatosis in graft histology. After a careful anamnesis, the etiology seemed to involve the high consumption of added sugars, particularly fructose-sweetened beverages.

Nonalcoholic steatohepatitis recurrence after liver transplant has been minimally reported in adults, but post-transplant steatosis has not been well-studied in pediatric liver transplant recipients.

As a result, the main goal of this study is to contribute to the knowledge of NAFLD in pediatric age and highlight the impact of obesity and high fructose diet on fatty liver development. The graft steatosis development suggests that metabolic dysregulation is capable of rapidly reproducing the disease in a healthy organ and that only a permanent diet change can prevent disease recurrence.

Abbreviations

ALT - Alanine aminotransferase

AMP - Adenosine monophosphate

AST - Aspartate transaminase

ATP - Adenosine triphosphate

BCAA - Branched-chain amino acids

BCKAD - Branched-chain α-ketoacid dehydrogenase complex

DQ - Developmental Quotient

GGT - Gamma-Glutamyl Transferase

IMP - Inosine monophosphate

IQ - Intelligence Quotient

MSUD - Maple Syrup Urine Disease

NAFLD - Nonalcoholic fatty liver disease

NASH - Nonalcoholic steatohepatitis

WHO - World Health Organization

WISC - Wechsler Intelligence Scale for Children

Keywords

Non-alcoholic fatty liver disease (NAFLD); fructose; Maple Syrup Urine Disease (MSUD).

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Introduction

Maple syrup urine disease (MSUD) is an autosomal recessive disorder characterized by defects in branched-chain α-ketoacid dehydrogenase complex (BCKAD), the second enzyme of the catabolic pathway of the three branched-chain amino acids (BCAA): leucine, isoleucine, and valine.[1]

MSUD has an estimated worldwide incidence of 1 case per 185 000 live births, but higher occurrences have been noted in populations with a high rate of consanguinity.[2] In Portugal, according to the report of the National Program for Early Diagnosis 2019, the estimated incidence of MSUD was 1: 83 534 newborns, with a higher prevalence among Roma people.[3]

The branched-chain amino acids are important precursors for various physiologic functions, such as protein synthesis, gluconeogenesis, fatty acid synthesis, cholesterol synthesis, and cellular signaling.[2] Within the brain, BCAA metabolism works to maintain glutamate levels, which plays an important role in brain development and cognitive functions, such as learning and memory.[2]

In the first step of the metabolism, BCAA are first converted into their respective alpha-ketoacids.[2] These intermediates then undergo oxidative decarboxylation, catalyzed by the BCKAD complex to yield isovaleryl-coenzyme A, alpha-methylbutyryl-CoA, and isobutyrl-CoA, which eventually result in acetyl-CoA, acetoacetate, and succinyl-CoA (figure 1).[1,2] The BCKAD complex is made up of several components, including subunits E1α and E1β, E2, and E3.[1,4] Maple syrup urine disease occurs due to a pathogenic defect in any BCKAD subunit, resulting in elevated BCAA in plasma, urine, and cerebrospinal fluid.[4] Allo-isoleucine, a metabolite of isoleucine, is a pathognomonic disease marker and it is invariably found in the blood of all patients with classic MSUD.[1,4] Among the BCAA metabolites, leucine appears to be the most neurotoxic.[4]

MSUD can have three different clinical presentations: a severe neonatal-onset form (the classic form) with acute metabolic decompensation and neurological distress; an acute, intermittent, late-onset form with recurrent episodes of metabolic decompensation during episodes of catabolic stress, such as intercurrent illnesses or increased protein intake; a chronic and progressive form presenting as hypotonia, failure to thrive, and developmental delay.[4] Classic MSUD is the most common and severe form of the disorder, resulting from less than 2% of BCKAD enzymatic activity.[1] Typically, after an initial symptom-free period, newborns present in the first week of life with poor feeding and drowsiness. At a more advanced stage, neurovegetative dysregulation with respiratory distress, apneas, bradycardia, and hypothermia

may appear. Neurological deterioration can be evidenced by changes in muscle tone and involuntary movements (opisthotonus, boxing, or pedaling movements). Coma may occur due to cerebral edema.[4] Concomitantly with the onset of the symptoms, the patient emits an intense sweet, malty, maple-syrup-like odor in organic fluids (such as cerumen and urine).[1,4] The toxicity is the result of damaging effects of leucine on the brain (with values above 2000 μmol/L), accompanied by severe ketoacidosis caused by the accumulation of the ketoacids.[1]

MSUD may be suspected in a newborn due to the presence of illness or an abnormal neonatal screening test result.[1] In our country, since 2005, routine newborn screening has been performed for MSUD. The most important diagnostic test is the measurement of plasma amino acid concentrations to evaluate for elevated levels of branched-chain amino acids (leucine, isoleucine, and valine) and allo-isoleucine. The identification of elevated alloisoleucine in plasma is suggestive of the diagnosis of MSUD.[2] The molecular study to confirm the disease is important for the diagnosis, genetic counseling of the family and allows a prenatal diagnosis.

The main pillars of short and long-term treatment include limiting the supply of natural proteins, decreasing protein catabolism, and stimulating protein synthesis. Episodes of metabolic decompensation must be treated aggressively. Plasma and tissue concentrations of leucine should be lowered rapidly. There are two types of procedures to eliminate toxic metabolites: exogenous clearance such as hemodialysis and peritoneal dialysis (in selected cases) or, more commonly, endogenous clearance, inducing anabolism through high energy intake with supplementation with BCAA-free formula and glucose infusion (with or without the addition of insulin).[4] Protein intake is typically discontinued for 24 to 48 hours.[2,4] Long-term management comprises a life-long diet in which proteins are supplied through a BCAA-free amino acid mixture and natural proteins according to tolerance. Most preparations also contain the recommended requirements for minerals, vitamins, and other essential nutrients. Additional fat and carbohydrates are provided according to the principles of the pediatric diet.[4] Valine and isoleucine should be supplemented to maintain basal necessities.[1]

Dietary therapy is the cornerstone of treatment and it can be the limiting step of good metabolic control if not strictly followed. Regular assessment of clinical and nutritional status provides the opportunity for psychological support and the monitoring of social and emotional needs since they are major issues of the therapy of the affected child and the family's wellbeing.[4]

Studies that assess the nutritional status of patients with Inherited Metabolic Diseases treated with low-protein diets reveal that overweight is not an uncommon condition since the reduction of protein intake can predispose the overconsumption of fats and carbohydrates.[5]

Nonalcoholic fatty liver disease (NAFLD) is an emerging entity, becoming the most prevalent pediatric chronic liver disease in Western Countries.[6,7] It includes a spectrum of

histological findings; initially, there is the development of liver lipid accumulation (presence of at least 5% of hepatocytes with fatty infiltration, not explained by another cause); then, the condition progresses over time with the development of steatosis with hepatocellular ballooning and inflammation (NASH), and it can potentially evolve to fibrosis and end-stage liver disease.[6,8]

Nowadays, it is recognized as the hepatic manifestation of metabolic syndrome, which is linked to obesity, insulin resistance, dyslipidemia, and cardiovascular disease.[6] Current lifestyle and diet modifications, which includes overconsumption of high-fat diet and increased intake of sugar-sweetened beverages, are major risk factors for the development of NAFLD.[6]

Hepatic fructose metabolization leads to hepatic steatosis and progression to fibrosis through mechanisms comparable to alcoholic liver disease.[6]

NAFLD is the most common cause of elevated liver enzymes in the pediatric population.[6] ALT is currently the recommended screening test: it is an inexpensive, minimally invasive, and universally available blood test.[9] For the diagnosis of NAFLD in children >10 years old, the use of two times the gender-specific ALT has 88% of sensitivity and 26% of specificity.[9] In the context of elevated ALT, higher AST, and higher GGT are associated with worse histology.[9] However, the biopsy is still the gold standard for diagnosis and accurate evaluation of fibrosis progression, and due to being an invasive method, it can limit its execution and underestimate this condition.[6]

Orthotopic liver transplantation can be an option reserved for patients with MSUD difficult to manage (liver is responsible for expressing 9-13% of BCKAD activity) or also for patients with NAFLD progressing to end-stage liver disease.[2,10,6]

NASH recurrence in allograft with the requirement of retransplantation can occur within a few months after transplantation if lifestyle changes are not attempted.[11,12,13,14]

Case report

This case report illustrates a male adolescent with a clinical diagnosis of classic MSUD. He was the second child of a non-consanguineous couple. He had a healthy, 4-year-old sister. Antenatal period and delivery of the baby were uncomplicated. He was born full-term, and the Apgar score was 8 at 1 minute and 10 at 5 minutes. He was at the 50th percentile for weight, 50th percentile for height and 85th percentile for head circumference. The physical examination was normal at birth.

At the age of 7 days, he was admitted to the hospital due to hypotonia, apnea, and poor feeding, with three days of evolution. On admission, he presented with hypoglycemia, metabolic acidosis, and ketonuria. He started fluid resuscitation and ventilatory support. The diagnosis of MSUD was based on elevated levels of plasma branched-chain amino acids, with leucine at 1889 µmol/L (reference values 47–109 µmol/L), isoleucine at 432 µmol/L (normal range 27–94 µmol/L), valine at 895 µmol/L (normal range 8-246 µmol/L), and allo-isoleucine at 257 µmol/L (normal range 1,2-3,4 µmol/L), whose result was known a day after admission.

The specific treatment of the disease was started immediately. The main objective of the acute phase treatment was to limit the accumulation of branched-chain compounds, mainly leucine, because it is the most neurotoxic. For that, temporary removal of natural proteins from the diet was done and an endogenous clearance was carried out through emergent therapy including glucose infusions, addition of insulin, and supplementation with BCAA-free formula. Leucine levels took six days to normalize, but in the third day of treatment, leucine values were less than 1000 umol/L.

On the discharge date, he was asymptomatic and was prescribed a long-term treatment which required a careful supply of calories, restriction of dietary BCAAs, and supplementation using a BCAA-free amino acid mixture, to provide adequate macronutrients, prevent catabolism, and maintain plasma BCAA within targeted treatment ranges. Basal leucine requirements were achieved using infant formula. Valine and isoleucine supplements were added to maintain metabolic homeostasis.

The final diagnosis of classic MSUD form was based on clinical presentation and biochemical data and confirmed with molecular study. They showed homozygous deletion of exons 2, 3 and 4 of the BCKDHA gene. The detected genomic loss caused a severe alteration of the reading frame, leading to practically null enzymatic activity.[15]

The patient had regular follow-up with a nutritional, metabolic, and neurocognitive assessment. At preschool age, metabolic control was good, with only a few episodes of

metabolic decompensation due to infectious complications. Neurocognitive development was age-appropriate (table I).

From the age of 3, he started to put on weight. At school age, he already had a weight above the 95th percentile (figures 2 and 3) and showed a deterioration in metabolic control with low educational achievement (learning difficulties), having an intelligence coefficient below average (table II). Although the parents were informed about the disease and the need to comply with dietary therapy, the patient made many dietary errors and did not comply with the nutritionist's meal plan.

During adolescence, he had an irregular compliance to the BCAA restricted diet and despite an absence of decompensations requiring hospital admission, serum leucine levels were persistently elevated (400-500 µmol/L). The patient lived a sedentary lifestyle and had obesity (BMI above the 97th percentile), hyperuricemia, hypertriglyceridemia, high blood pressure, insulin resistance, and showed a mild cognitive delay (IQ<70).

As a reduction of leucine levels was not accomplished through diet adjustments, by the age of 11 the boy was referenced to the Pediatric Gastroenterology Unit of our hospital to be proposed for a liver transplant. Determinations of slightly elevated transaminases have been found previously, and attributed to infectious complications, but after 9 years old he had persistently elevated values (figure 4). Abdominal ultrasound showed diffuse hepatic steatosis. Liver histology confirmed macro-vesicular steatosis and portal fibrosis, but no evidence of cirrhosis. As the changes found are not part of the MSUD manifestations, a study to exclude liver diseases such as autoimmune liver disease, hepatitis B and C, Alpha-1 Antitrypsin Deficiency and Wilson's disease was done. No other steatohepatitis cause was identified beyond a suspected Wilson's Disease. The workup for this disease included serum ceruloplasmin (18,2 mg/dL; reference values 16–36 mg/dL), hepatic copper concentration (112,27 µg/g of tissue; reference values 10-35 µg/g), and ophthalmologic evaluation to look for Kayser-Fleischer rings (absent). Genetic testing found a variant in the ATP7B gene - c.1607T>C (p.Val536Ala) - which in a heterozygous state is probably benign.

The patient underwent a liver transplant at the age of 13 (young cadaveric donor, graft without steatosis). After that, the patient had noticeable decrease branched-chain amino-acids (leucine went from 500 to 150 µmol /L) and allo-isoleucine, despite the increase of the proteins in the diet. However, two months later he showed elevated transaminases (ALT increased four times the reference value, and AST and GGT twice the reference values), hyperuricemia (although lower than pre-transplant), and hypertriglyceridemia. The graft histology revealed 40% steatosis. No apparent cause was identified, except for high consumption of added sugars,

particularly sugar-sweetened beverages (> 100g/day). Parents revealed some difficulty in controlling food intake since he had free access to sugary drinks at the school buffet.

Seven months after transplantation, after nutritional optimization with fructose reduction and increase in daily physical activity, the patient revealed an 85−97th percentile BMI, normal transaminases, normal triglycerides, and a significant steatosis reduction to 15-30% in histology.

Discussion

This patient had a typical presentation of a neonatal form of MSUD. The symptoms started on the fourth day of life and the patient was admitted with hypotonia, apnea, and poor feeding. The diagnosis was based on the clinical history and elevated plasma BCAA levels. Molecular studies showed a large deletion of the BCKDHA gene.

Early diagnosis of these situations and prompt treatment is essential for prevent or at least minimize the dysfunction of the central nervous system.[4] For normal cognitive development, the most important thing is the rapidity of the decrease in leucine levels below the critical value of 1000 µmol/L.[16]

This patient was diagnosed on the seventh day of life, emergency treatment was started, but he took a few days to lower the leucine levels. Neonatal screening for this pathology started in Portugal only in the following year (2005).[17]

In early childhood, the dietary treatment allowed favorable control of the metabolic disease, while ensuring adequate growth and a positive neurocognitive outcome.

In Inherited Metabolic Disorders, it is commonly described that dietary adherence deteriorates from the age of 10 years onwards, representing the transition of responsibility from the principal caregivers to the patients.[18] But in this case, as the family was permissive, the problems started earlier.

Despite dietary therapy being considered the most appropriate option in most patients because of the higher risks and potential long-term complications of a liver transplant, this patient had irregular compliance with BCAA restricted diet and serum leucine levels were gradually increasing. Poor metabolic control was probably responsible for his cognitive delay because long-term neurocognitive effects are related to the quality of longitudinal metabolic control.[19]

He also developed clinical conditions which are part of a well-defined cluster known as metabolic syndrome such as obesity (defined as a BMI at or above the 95th percentile), hypertriglyceridemia (>150 mg/dL), high blood pressure, insulin resistance, and NAFLD.[20]

In this patient, liver transplant was performed to accomplish better metabolic control and spare his cognitive functions, which was achieved.

Unfortunately, poor eating habits continued after liver transplant. When the diet was revised, the patient had a high consumption of added sugars, particularly fructose-sweetened beverages.

The recurrence of NAFLD in this young patient seemed to be linked to the increase of fructose consumption, which causes a comparable pattern of liver injury to alcohol

consumption. Thus, fructose is believed to have a similar addiction effect, named by some authors as “fructoholism”, potentially leading to “fructoholic" liver diseases.[6]

Fructose has been linked to NAFLD pathogenesis due to the distinct characteristics of its metabolism and deleterious effects on metabolic pathways (figure 5).[21] Excessive and chronic consumption of fructose in this patient probably had hepatic repercussions leading to *de novo* lipogenesis. After high consumption of fructose, by saturating the glycolytic pathway, there is an accumulation of glycolysis intermediates which can be converted to glycerol-3-phosphate used in triglyceride synthesis.[22] Additionally, chronic intake of fructose acts as an inductor of *de novo* lipogenesis by activating several key transcription factors, such as Sterol Response Element Binding Protein 1c (SREBP1c).[6,22]

On the other hand, the excessive consumption of fructose can also explain the high levels of uric acid in this patient. Liver fructose is rapidly metabolized, consuming adenosine triphosphate (ATP), which may result in increased adenosine monophosphate (AMP) and inosine monophosphate (IMP) and conversion of IMP to uric acid (figure 5).[7] In turn, uric acid causes oxidative stress, contributing to the development of his liver injury.[22]

Fructose-induced non-alcoholic fatty liver disease is also associated with changes in microbiota composition that leads to a compromised intestinal barrier, with translocation of bacterial compounds into portal vein, and consequently increased oxidative stress (gut-liver axis dysfunction).[6,22]

The graft steatosis development suggests that metabolic dysregulation is capable of rapidly reproducing the disease in a healthy organ (histology of the donor liver was reviewed and it revealed a graft with no steatosis). Significant changes in the levels of transaminases (figure 4) in the post-transplant period raised the hypothesis of recurrence of nonalcoholic steatohepatitis. The patient underwent a liver biopsy which confirmed the diagnosis.

The problem of recurrence of NASH in the transplanted liver has been reported before.[13] Previous metabolic co-morbidities and worsening of metabolic profile post-liver transplant are the main drivers of NASH recurrence.[23]

Fortunately, early recognition of this situation allowed steatosis reversibility. Even though the decrease in ALT is often used as a non-invasive marker of improved NAFLD histology and there is some evidence to support its use in pediatric clinical trials, liver biopsy remains the best method available.[9] Therefore, the patient performed it again.

A fructose-restricted diet in this patient was associated with improvement of serum markers of liver dysfunction and cardiometabolic risk, with significant reduction of alanine aminotransferase (figure 4), triglycerides, and abdominal obesity (demonstrated by reducing waist circumference).

Currently, the consumption of sugars, particularly sugar-sweetened beverages in European and American children and teenagers exceeds recommendations.[24] WHO recommends limiting the intake of free sugars to <10% of total energy intake and suggests that a reduction to <5% would have additional benefits.[24] This represents 15 to 28 g of free sugars for girls and 16 to 37 g for boys, according to age. The American Heart Association recommendation is based on a fixed value of 25 g of added sugar for all children 2-19 years of age, not taking into account the different levels of intake across this wide age range.[25] It is important to note that if a child drinks from a can of 330 ml of sugary drink it is already exceeding the recommended daily consumption (one unit can contain about 35 grams of sugar).

For all these reasons, it is crucial to adopt strategies to prevent excessive sugar intake in a particularly vulnerable population - the pediatric population. However, the sugar industry is powerful, it has great means installed, whether through political lobbying, funding studies on health policies, or mass manipulation.

More recent measures, such as a ban on the sale of products rich in added sugars, in school and hospital buffets and canteens need an adequate inspection for compliance; also, products will continue to be available in private establishments close to these institutions.[26]

Some authors propose another type of potential measures, some of which have already been successfully implemented: food education at school to promote knowledge about nutrients and the importance of them to achieve a healthy diet, increase in daily physical activity, regulation of the amount of sugars added by food industries, and limitations on screen time activities to fewer than 2 hours per day.[6,9] Furthermore, the World Health Organization, through the Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013-2020, considers important to add taxes on foods that contain any form of added sugar and create subsidies for behaviors associated with improved health outcomes.[6]

Demystifying marketing campaigns of the sugar industry can also be used as a preventive weapon. A good example is given by the *SugarScience* website: a project developed by a team of health scientists from the University of California, San Francisco, which is an authoritative source of evidence-based scientific information about sugar and its impact on health. The main goal is to take this information out of medical journals and make it available to the public, through easy-to-understand scientific articles and flyers with assertive messages.[27] An example is shown in figure 6.

It is clear this patient was inserted in a specific clinical context, which made it difficult to manage the diet, but the general recommendations and regular follow-up by a multidisciplinary team will certainly have beneficial long-term outcomes. Besides that, parental involvement is important for a more solid behavior change to achieve a healthier lifestyle.[6]

Conclusion

This case highlights the impact of obesity and a high-fructose diet on the development of non-alcoholic fatty liver disease. In addition, it shows the recurrence of non-alcoholic steatohepatitis after liver transplantation (as a therapeutic measure of the underlying metabolic disease - MSUD). The graft steatosis development suggests that poor metabolic control is capable of rapidly reproducing the disease in a healthy organ.

NAFLD is an emerging entity in the pediatric age, becoming the most prevalent pediatric chronic liver disease. Overconsumption of a high-fat diet and increased intake of sugar-sweetened beverages (namely fructose) are major risk factors for the development of non-alcoholic steatohepatitis.

It is expected that children diagnosed with NAFLD at present will become adults with terminal liver disease in the future. Liver transplant cannot be seen as a definitive treatment, on the one hand, due to the risks it entails and on the other, the risk of disease recurrence if lifestyle changes are not attempted. Thus, NAFLD aspires to be one of the biggest public health problems on a global scale, with consequences on the quality of life of the populations and high monetary expenditures due to the progression of the disease.

Finally, NAFLD urgently needs adequate intervention, more than raising the awareness of the younger population and family members, it requires implementation of public health measures by governments to prevent excessive sugar intake.

Appendix

Table I: Developmental Quotient of the patient using Griffiths Mental Development Scale. To calculate the overall DQ, the patient's age of development (sum of the various domains) was divided by the chronological age and multiplied by 100.

Age (years)	Developmental Quotient (DQ)
2	97
6	94

Table II: Intelligence Quotient of the patient using WISC-III Classification.

Age (years)	Intelligence Quotient (IQ)	WISC-III Classification
7	87	Low average
9	76	Borderline
13	65	Mild mental retardation

Figures

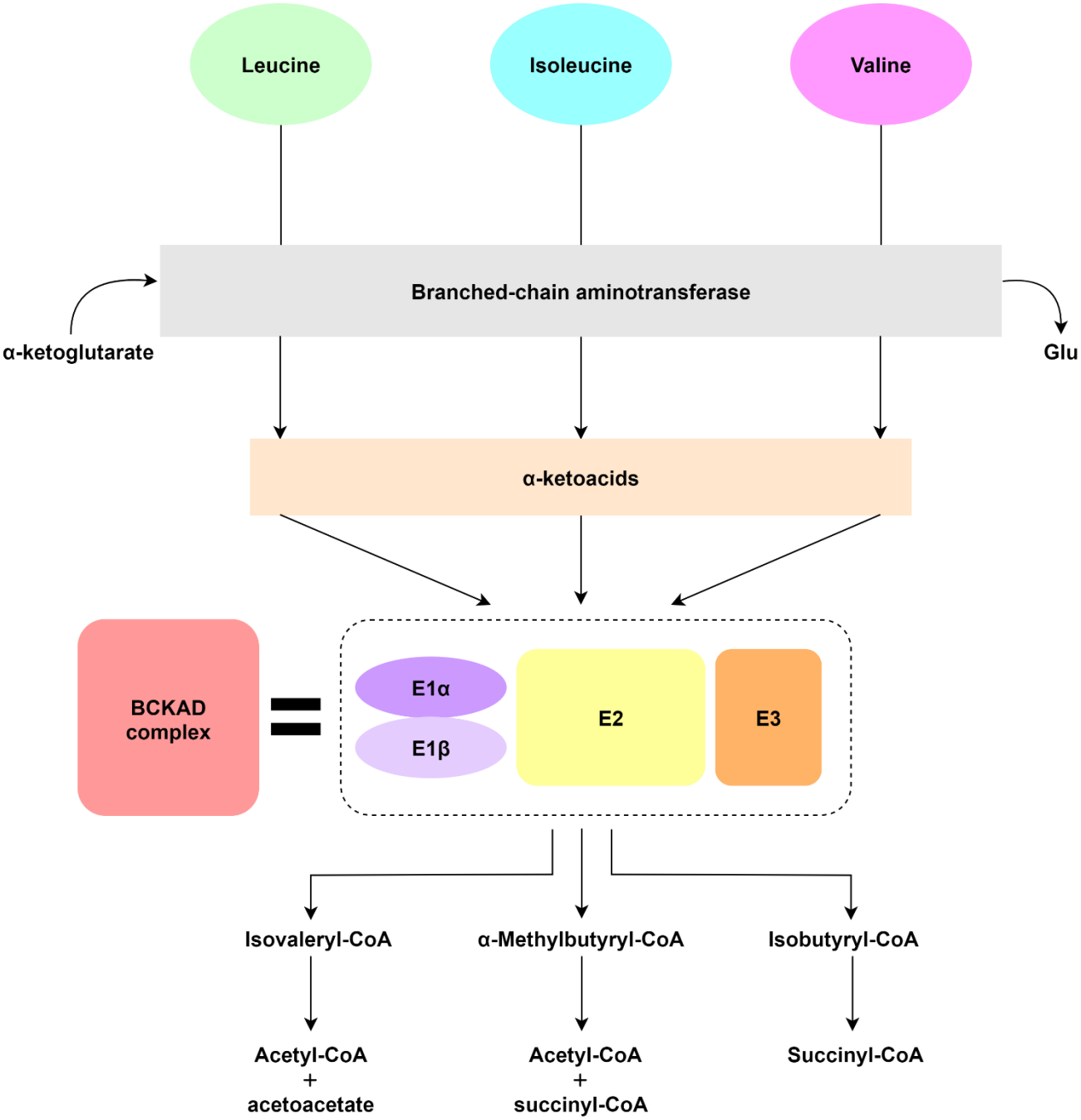
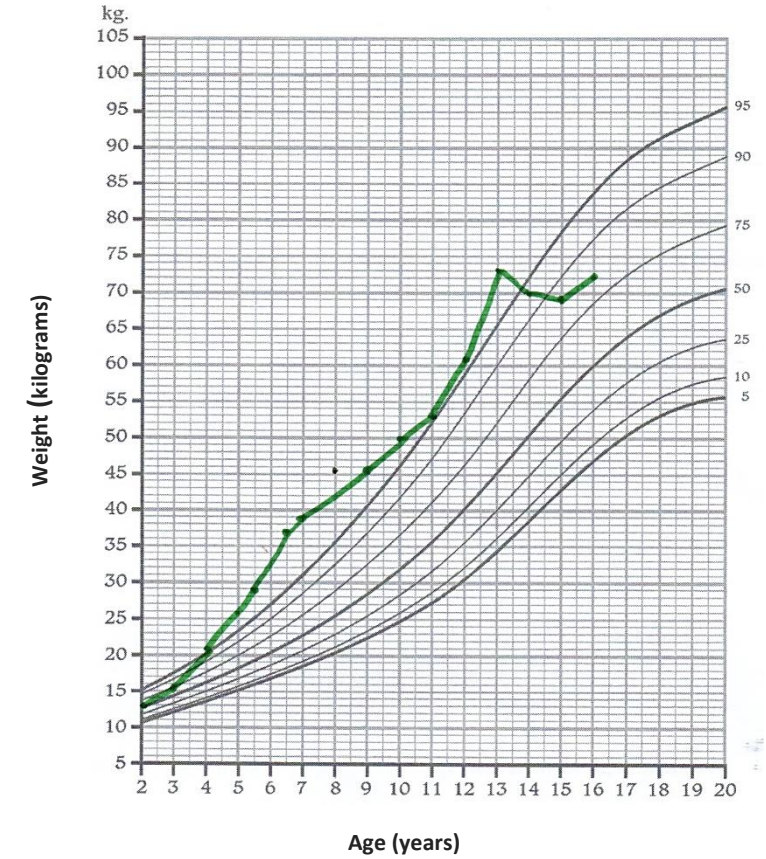
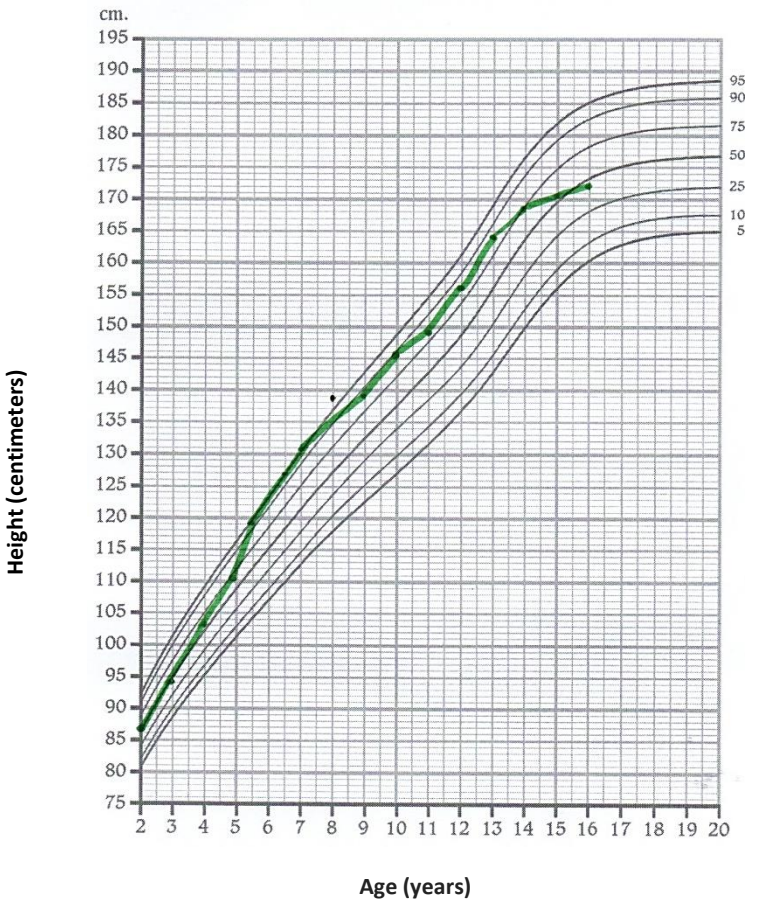


Figure adapted from the article "Maple syrup urine disease: mechanisms and management".[1]

Figure 1: Schematic overview representation of BCAA catabolic pathway. The BCAAs undergo transamination that is catalyzed by the branched-chain aminotransferase and requires α-ketoglutarate, leading to the production of the α-ketoacids. These intermediates then undergo oxidative decarboxylation, catalyzed by the BCKAD complex.

Abbreviations: Glu, glutamate; BCAAs, branched-chain amino acids; BCKAD, branched-chain α-ketoacid dehydrogenase.





Figures 2 and 3: Patient growth charts (weight on top, height on bottom). Sourced from his Child and Youth Health Book.

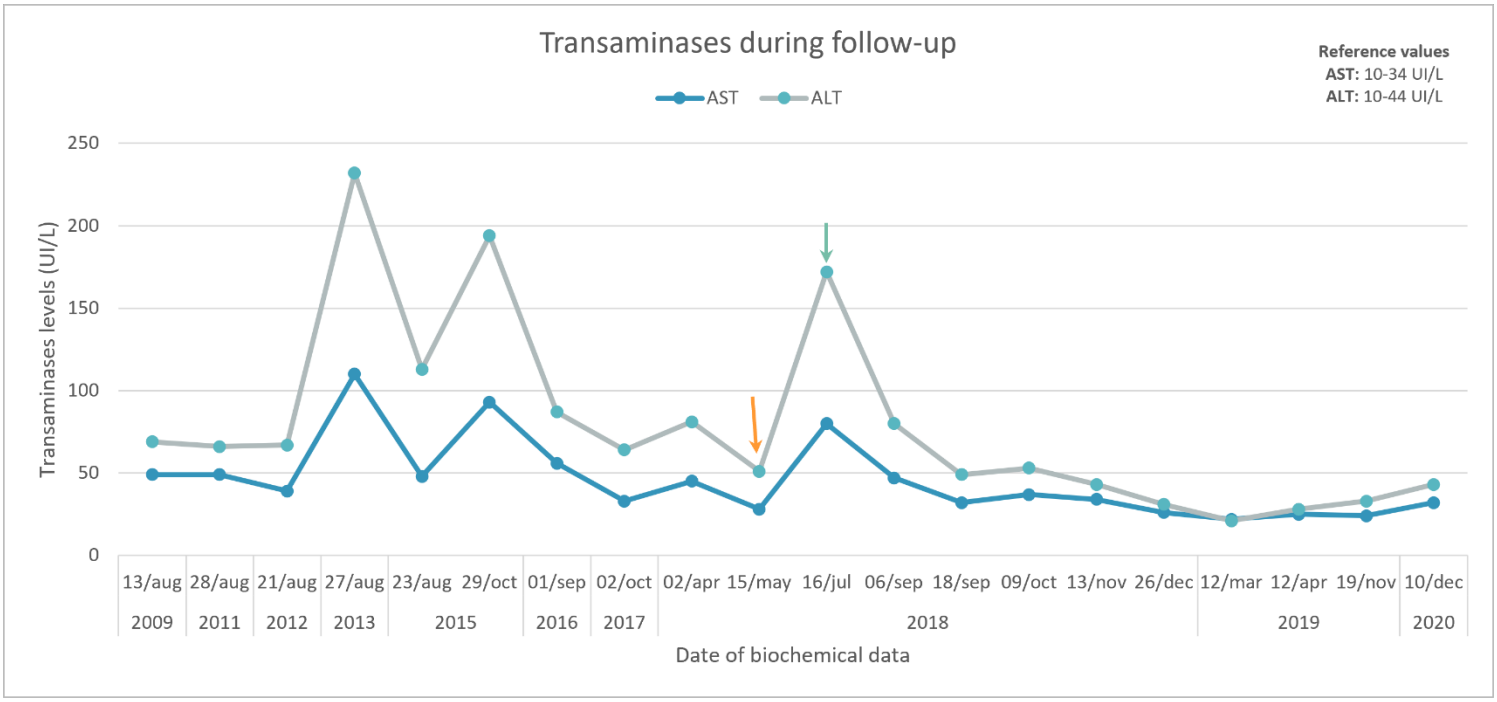


Figure 4: Transaminases profile evolution during follow-up. Determinations of slightly elevated transaminases have been found since 2009 and attributed to infectious complications, but after 9 years old he had persistently elevated values. Liver transplantation is represented with an orange arrow. A substantial increase in transaminases is noted about 2 months after transplantation. After nutritional modification (green arrow), a marked decrease in the parameters of liver injury is visible. Normal range of transaminases has been maintained over time.

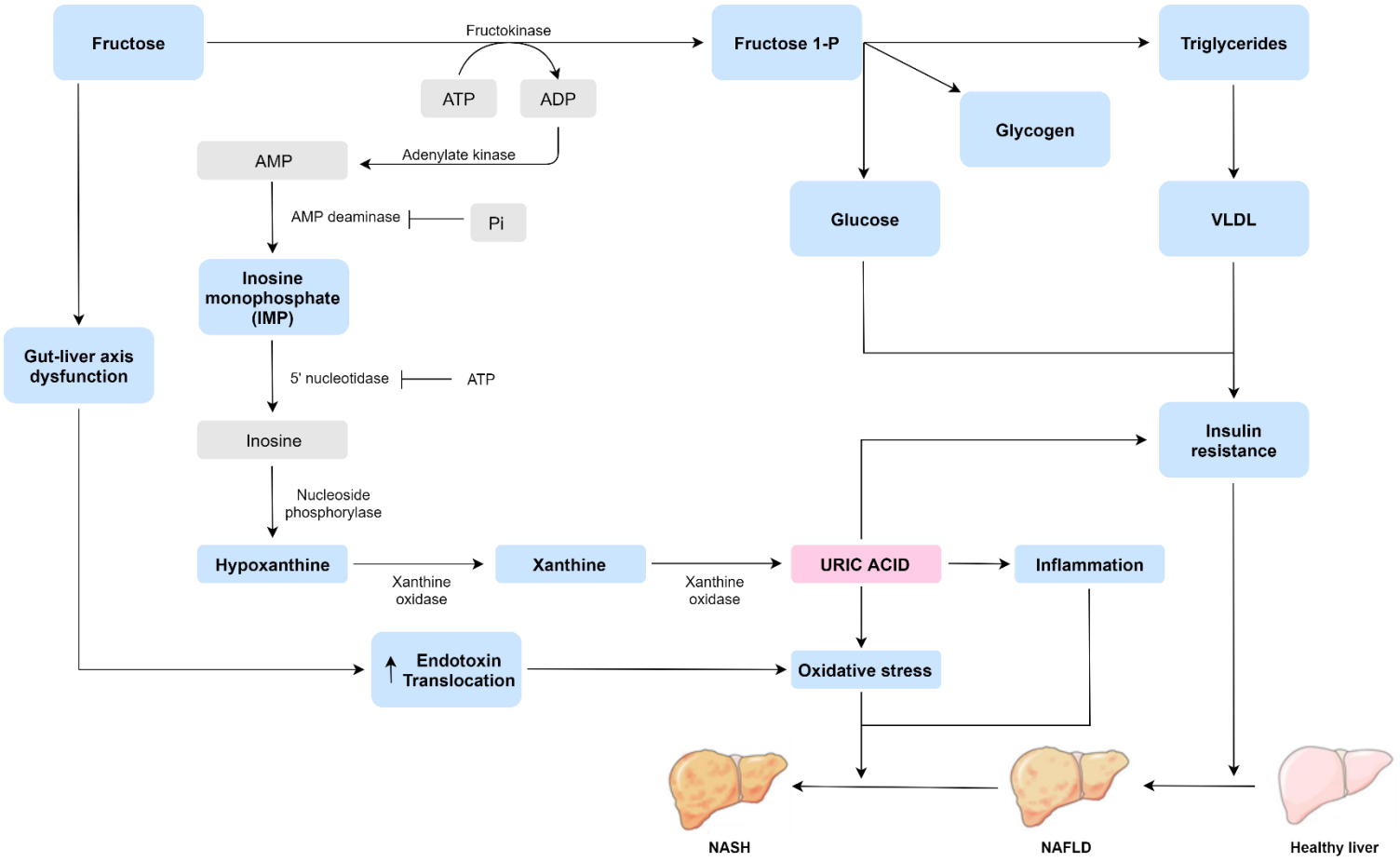


Figure adapted from the article "Serum uric acid concentrations and fructose consumption are independently associated with NASH in children and adolescents".[7]

Figure 5: Schematic representation of the role of dietary fructose in Nonalcoholic Fatty Liver Disease.

Figure 6: Infographics sourced from *SugarScience* (the unsweetened truth).[27]

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