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Food triggers and inherited metabolic disorders: a challenge to the pediatrician

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Abstract

Several disorders should be considered in the case of newborns and infants experiencing acute or recurrent symptoms after food ingestion. Immune-mediated adverse food reactions are the most frequent and always to be considered. Nevertheless, in the extensive differential diagnosis, clinicians should also include inherited metabolic disorders (IMDs). This review reports clinical features and diagnostic aspects of the most common IMDs that may present with acute manifestations triggered by food intake. Major focus will be amino acid and protein metabolism defects and carbohydrate disorders.

Nowadays, for many of these disorders the risk of an acute presentation triggered by food has been decreased by the introduction of expanded newborn screening (NBS). Nevertheless, clinical suspicion remains essential because some IMDs do not have still reliable markers for NBS and a false negative screening result may occur.

The aim of this review is to help pediatricians to take these rare inherited disorders into account in the differential diagnosis of acute or recurrent gastrointestinal symptoms related to food intake, which may avoid delayed diagnosis and potentially life-threatening consequences.

Keywords: Inherited metabolic disorders, Late-onset presentation, Food triggers, Adverse food reactions

Background

Several disorders should be considered in the case of newborns and infants experiencing acute or recurrent symptoms after food ingestion: motility disorders or anatomic abnormalities of the gastrointestinal tract, infections, systemic diseases and adverse food reactions are the most frequent and always to be considered [1].

Adverse reactions to food, excluding toxic reactions, are distinguished on the basis of the pathogenetic mechanism and may be either immune-mediated or non-immune-mediated (Fig. 1). Immunological food reactions are the most common, including IgE-mediated and non-IgE-mediated food allergies, and coeliac disease. Nevertheless, non-immunological food reactions, such as secondary food sensitivities and food intolerances, may also play an important role [2–4].

Adverse food reactions due to secondary food sensitivities occur with or after the effects of other conditions (e.g.,

secondary to gastrointestinal disorders or secondary to drug treatment) [4].

Food intolerances can originate from the pharmacological effects of vasoactive substances present in foods (e.g., histamine) or from enzymatic or transport defects. In rare cases, the pathogenetic mechanism remains undefined, and the reactions are classified as idiosyncratic [3, 5].

Enzymatic or transport food intolerances can occur due to defects of enzymes or transporters specifically located in the digestive system (e.g., carbohydrate intolerances) [5] or due to systemic defects of enzymes or transporters of specific metabolic pathways (inborn errors of metabolism) [6].

Inherited metabolic disorders (IMDs) are a complex and heterogeneous group of rare monogenic disorders, usually resulting from a deficient activity in a single pathway of intermediary metabolism [7].

Each IMD is individually rare, but data from expanded newborn screening (NBS) programs outlines an estimated incidence of 1:1500–5000 [8, 9].
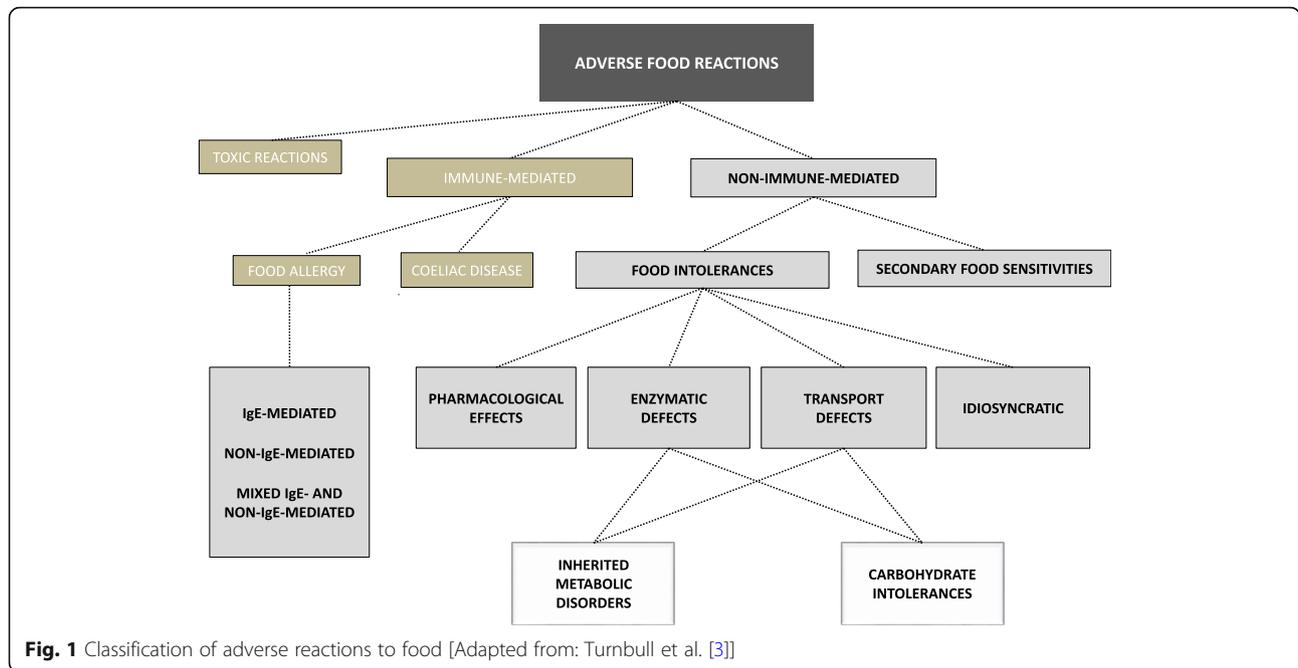
Although the most severe forms present usually in the neonatal period, late-onset presentations may represent

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Fig. 1 Classification of adverse reactions to food [Adapted from: Turnbull et al. [3]]

an important cause of morbidity and mortality in the pediatric age [10].

Food may be a specific trigger of metabolic decompensation at any age.

This review reports clinical features and diagnostic aspects of the most common IMDs that may present with acute manifestations triggered by food intake. Major focus will be amino acid and protein metabolism defects and carbohydrate disorders.

The aim of this review is to help pediatricians to take these rare inherited disorders into account in the differential diagnosis of acute or recurrent gastrointestinal symptoms related to food intake, which may avoid delayed diagnosis and potentially life-threatening consequences.

Disorders triggered by proteins
Case presentation 1

The patient was born at term after an uneventful pregnancy from two unrelated parents. The baby was exclusively breast-fed until six months of age. Soon after the start of weaning, between the ages of 6 and 12 months, he experienced repetitive vomiting and episodes of diarrhea, approximately within 1 to 3 h after the consumption of meat, chicken, fish, and egg. Since symptoms always recurred after the administration of the same foods, an allergic problem was suspected. Food protein-induced enterocolitis (FPIES), a non-IgE-mediated gastrointestinal disorder, was diagnosed. Protein-rich foods related to the symptoms were eliminated from his diet and were not subsequently reintroduced because the patient manifested a severe aversion to these foods.

At 7 years, clinical examination revealed short stature, mild language retardation and hepatosplenomegaly. Laboratory tests showed high serum ferritin (770 ng/ml), and lactic dehydrogenase (LDH) values (1007 UI/L) with normal white blood cell, erythrocyte and platelet counts.

Other laboratory tests (including blood gases and ammonia) were all in the normal range.

Bone marrow aspirate examination revealed evidence of erythrophagocytosis (HP).

Then, due to the clinical features and the dietary history of recurrent vomiting and spontaneous protein-rich food aversion, plasma and urinary amino-acid analysis were performed.

We found lower than normal plasmatic levels of lysine, ornithine, and arginine, and higher than normal urinary levels of the same amino acids. Based on the results, we diagnosed lysinuric protein intolerance (LPI). The diagnosis was confirmed by molecular analysis of SLC7A7 gene. The patient started a controlled low-protein diet and an oral treatment with sodium benzoate and citrulline [11].

Case presentation 2

A male 15 months of age was admitted to the hospital after a day of persistent vomiting and somnolence alternating with periods of irritability. He had a history of recurrent vomiting by the 6 months of age. According to his parents, the child had no spontaneous aversion to proteins (daily intake 2.5 g/kg) and the episodes seemed to be more related to fructose ingestion even the child used to have a meal including fruit and meat together. Routine biochemical investigations performed in well-state showed elevated

Table 1 Diagnostic features and management of the most common IMDs triggered by proteins

	Disorders triggered by proteins				
	UCDs	LPI	OAs	MSUD	HI/HA
Newborn screening	Distal defects	No	Yes	Yes	No
Food triggers	Protein load	Protein load	Protein load	Protein load	Protein load (leucine sensitivity)
Age of onset	Variable. From a few days after birth (complete enzymatic deficiencies) to adult age (partial enzymatic deficiencies)	Variable. Common during weaning	Variable. From a few days after birth (complete enzymatic deficiencies) to adult age (partial enzymatic deficiencies)	Variable. From a few days after birth (complete enzymatic deficiencies) to adult age (partial enzymatic deficiencies)	After the first few months of life
Main presenting features	Acute or episodic encephalopathy with lethargy and vomiting, liver failure, spontaneous protein aversion	Recurrent emesis and/or diarrhea, episodes of postprandially altered mental status. Strong aversion to high-protein foods by the age of 1 year	Acute or episodic encephalopathy with lethargy and vomiting	Acute or episodic encephalopathy with lethargy and vomiting. Maple syrup odor	Recurrent episodes of profound hypoglycemia induced by fasting and protein-rich meals
Main routine laboratory findings	Hyperammonemia	Postprandial hyperammonemia, high levels of LDH and ferritin, hypertriglyceridemia	Ketoacidosis, hyperammonemia, hyperlactatemia	Ketoacidosis	Persistent mild or moderate hyperammonemia, recurrent hypoketotic hypoglycemia
Diagnostic confirmation	Plasma amino acid analysis, urinary orotic acid dosage. Genetic testing	Plasma and urinary amino acid analysis. Genetic testing	Urinary organic acid analysis, plasma acylcarnitine profile. Genetic testing	Plasma amino acid analysis, urinary organic acid profile. Genetic testing	Genetic testing
Acute management	Specialist centre. Stop protein intake, ammonia detoxification, measures to reverse catabolism	Specialist centre. Stop protein intake, ammonia detoxification, measures to reverse catabolism	Specialist centre. Stop protein intake, ammonia detoxification, measures to reverse catabolism	Specialist centre. Stop protein intake, leucine and BCKAs detoxification, measures to reverse catabolism	Specialist centre. Prompt correction of hypoglycemia
Chronic management	- Protein-restricted diet - adequate energy intake - ammonia scavengers - oral arginine or citrulline supplementation - liver transplantation for selected patients	- Protein-restricted diet - adequate energy intake - ammonia scavengers - oral lysine and citrulline supplementation	- Protein-restricted diet - adequate energy intake - ammonia scavengers - defect-specific amino acids supplementation - liver/kidney transplantation for selected patients	- Protein-restricted diet - adequate energy intake - oral isoleucine and valine supplementation - liver transplantation for selected patients	- Protein-restricted diet - oral diazoxide
Natural history	Variable. The duration and severity of hyperammonemia strongly correlate with brain damage. Late complications may be fatal	Variable. The duration and severity of hyperammonemia strongly correlate with brain damage. Late complications may be fatal	Variable. The duration and severity of acidosis and hyperammonemia strongly correlate with brain damage. Late complications may be fatal	Variable. The duration and severity of coma strongly correlate with brain damage	Variable. The duration and severity of hypoglycemias strongly correlate with brain damage. Increased frequency of generalized seizures

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Main presenting biochemical features		IMDs potentially triggered by proteins	Main differential diagnosis
KETOSIS	WITH METABOLIC ACIDOSIS	OAs (e.g., MMA, PA, IVA) MSUD	FBPase deficiency* Glycogen storage disorders (Ia)* Congenital lactic acidemias (e.g., respiratory chain defects, PC, MCD) Ketolytic defects Diabetes Intoxication
	WITHOUT METABOLIC ACIDOSIS	MSUD (acidosis may be mild or absent in neonatal age and early infancy)	Glycogen storage disorders (0, III, VI, IX)* Ketolytic defects **Fasting, catabolism, vomiting** **Ketotic hypoglycemia** MCT-enriched diet and ketotic diets GH deficiency/hypopituitarism Adrenal disorders
HYPERAMMONEMIA	WITH METABOLIC ACIDOSIS	OAs (e.g., MMA, PA, IVA) MSUD UCDs (acidosis is usually not severe)	Congenital lactic acidemias (e.g., respiratory chain defects, MCD, PC) GAII* FAODs (acidosis is usually not severe)* Intoxication Reye syndrome Liver failure
	WITHOUT METABOLIC ACIDOSIS	UCDs LPI MSUD (acidosis may be mild or absent in neonatal age and early infancy) HI/HA*	FAODs* Liver failure

Fig. 2 Diagnostic algorithm to guide the initial approach to IMDs triggered by proteins, based on the main presenting biochemical features (ketosis and hyperammonemia with or without metabolic acidosis). IMDs not triggered by proteins but with similar biochemical features are shown as differential diagnosis. Abbreviations: *FAODs* fatty acid oxidation defects, *FBPase deficiency* fructose-1,6-bisphosphatase deficiency, *GAII* glutaric acidemia type II, *GH* growth hormone, *HI/HA* hyperinsulinism hyperammonemia syndrome, *IVA* isovaleric acidemia, *LPI* lysinuric protein intolerance, *MCD* multiple carboxylase deficiency, *MCT* medium-chain triglycerides, *MMA* methylmalonic acidemia, *MSUD* maple syrup urine disease, *OAs* organic acidurias, *PA* propionic acidemia, *PC* pyruvate carboxylase, *UCDs* urea cycle disorders. * hypoglycemia is usually the main presenting symptom

transaminases (AST 300 U/L, ALT 1727 U/L), normal ammonia, lactate, amino acids and acylcarnitine profiles. Isoelectric focusing (IEF) of serum transferrin (Tf) showed an increased trisialo-Tf form, suggesting a possible diagnosis of fructosemia.

The patient was put on a low-fructose diet and molecular analysis for aldolase B gene mutation was performed.

About 4 months later, he was readmitted to the hospital with severe acute encephalopathy after a day of continuous vomiting. Vomiting was started by the ingestion of a sandwich with ham.

Brain CT scan showed severe edema. Liver transaminases were increased (AST 557 U/L, ALT 1923 U/L); ammonia reached a value of 600 μmol/L. Despite intensive treatments, the child died the following morning. Plasma amino acids and urinary organic acids performed during acute symptoms were suggestive for ornithine transcarbamylase deficiency (OTCD). OTC gene analysis confirmed the diagnosis [12].

Deficiencies of enzymes or transporters involved in amino acid and/or protein metabolism may present acutely in the neonatal period, typically after a short symptom-free interval, or later in life with acute, intermittent or progressive forms. In all cases, clinical features become apparent as a result of the accumulation of toxic compounds proximal or related to the metabolic block (intoxication type disorders) [10]. The most common acute (or recurrent) signs of "intoxication" are vomiting or feeding difficulties with lethargy, encephalopathy that may rapidly progress to coma, and liver failure [10].

Triggers provoking acute metabolic attacks are more commonly catabolic states (e.g., prolonged fasting, infections, fever, surgery, chemotherapy, high-dose glucocorticoids). Nevertheless, an increased protein intake (e.g., weaning dietary changes, a barbecue) may also be a cause of metabolic decompensation both in children and in adults [13].

Adult-onset cases unmasked by parenteral nutrition have also been described [14, 15].

Acute manifestations triggered by protein-rich food intake may be observed in patients with urea cycle disorders (UCDs) [13, 16, 17], lysinuric protein intolerance (LPI) [11, 18], organic acidemias (OAs) [16, 19], and maple syrup urine disease (MSUD) [20] (Table 1). Intoxication is caused by ammonia (UCDs, LPI), toxic organic acids (OAs) or amino acids and related toxic compounds (MSUD). Hyperinsulinism/hyperammonemia syndrome (HI/HA) may be included in the group of disorders

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Table 2 Diagnostic features and management of the most common IMDs triggered by sugars

	Disorders triggered by sugars		
	CG	Generalized GALE	HFI
Newborn screening	Yes	Yes	No
Food triggers	Breast milk, infant formulas and foods containing galactose or lactose	Breast milk, infant formulas and foods containing galactose or lactose	Fructose-, sucrose-, and sorbitol-containing foods
Age of onset	Within a few days after breastfeeding or when lactose-containing formula feeding is started	Within a few days after breastfeeding or when lactose-containing formula feeding is started	At the time of weaning or after supplementary food
Main presenting features	Poor feeding, vomiting, hepatomegaly, jaundice, liver failure, sepsis, cataracts	Poor feeding, vomiting, hypotonia, hepatomegaly, jaundice, liver failure, cataracts	Vomiting, postprandial hypoglycemia, progressive liver dysfunction, aversion to fructose-containing foods and sweets
Main routine laboratory findings	Liver damage, increased plasma galactose, urinary reducing substances	Liver damage, increased plasma galactose, urinary reducing substances	Hypoglycemia, urinary reducing substances. Metabolic acidosis, liver and kidney damage in severe cases
Diagnostic confirmation	Erythrocyte GALT enzyme activity, erythrocyte galactose-1-phosphate concentration. Genetic testing	Erythrocyte GALE enzyme activity, erythrocyte galactose-1-phosphate concentration. Genetic testing	IEF of Tf. Genetic testing
Acute management	Specialist centre. Lactose-free infant formula	Specialist centre. Lactose-free infant formula	Specialist centre. Prompt correction of hypoglycemia
Chronic management	Lactose-free, galactose-restricted diet throughout life	Lactose-free, galactose-restricted diet throughout life.	Fructose-, sucrose-, and sorbitol-restricted diet. Vitamin C supplementation
Natural history	Extreme variability in long-term outcome. Dyspraxias, learning disabilities, mental retardation, ataxia, tremors, and premature ovarian insufficiency in females may be present	Limited long-term outcome data. No evidence of premature ovarian insufficiency in females	Benign disease if appropriately diagnosed and treated

triggered by proteins, because hypoglycemias are usually unmasked by protein-rich meals (leucine sensitivity) [21–23]. Nevertheless, HI/HA does not belong to intoxication type disorders group, being a very rare form of congenital hyperinsulinism (CHI) [24].

Based on few laboratory data (ketones, ammonia, blood gas analysis) collected at the same time during the acute attack, we propose a schematic diagnostic algorithm to guide the initial approach and the differential diagnosis of acute presentations of IMDs triggered by proteins (Fig. 2) (Table 1).

Nowadays, for many of these IMDs the risk of an acute presentation triggered by food has been decreased by the introduction of expanded NBS.

NBS may detect distal UCDs *(citrullinemia type 1 or argininosuccinate synthetase deficiency [ASSD, OMIM #215700], argininosuccinic aciduria or argininosuccinate lyase deficiency [ASLD, OMIM #207900] and arginase 1 deficiency or argininemia [ARG1D, OMIM #207800]),* and citrullinemia type 2 or citrin deficiency (Citrin-D, OMIM #605814 and #603471), a mitochondrial transport defect of the urea cycle.

Proximal enzymatic defects of the urea cycle *(carbamoyl-phosphate synthase 1 deficiency [CPS1D, OMIM #237300], ornithine transcarbamylase deficiency [OTCD, OMIM #311250] and N-acetylglutamate synthase deficiency [NAGSD, OMIM #237310]),* and lysinuric protein intolerance (LPI, OMIM #222700) are not usually included in the screening panel, because of the low specificity and sensitivity of NBS marker (hypocitrullinemia) [25]. However, screening metabolites kits including orotic acid and/or glutamine assay have been proposed to identify patients with OTCD, as well as with other UCDs [26, 27].

NBS may also detect OAs *(e.g., propionic acidemia [PA, OMIM #606054], methylmalonic acidemia [MMA, OMIM #251000], isovaleric acidemia [IVA, OMIM #243500] and glutaric acidemia type 1 [GA1, OMIM #231670]* and maple syrup urine disease [MSUD, OMIM #248600]). OAs result from a defect in the branched-chain amino acids (BCAAs) or lysine catabolism [28–30], leading to a specific NBS acylcarnitines pattern [31–33]. MSUD is also due to a defect in the metabolic pathway of the BCAAs [20], which leads to high levels of BCAAs and alloisoleucine [34].

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			IMDs potentially triggered by food	Main differential diagnosis
HYPOGLYCEMIA	**WITH PERMANENT HEPATOMEGALY**	**POSTPRANDIAL**	**CG and GALE HFI**	
		AT FAST		Glycogen storage disorders (Ia-1b, III, VI, IX) FBPase deficiency FAODs
		UNPREDICTABLE		CDG type 1a-1b (due to hyperinsulinism)
	WITHOUT PERMANENT HEPATOMEGALY	**KETOSIS** **POSTPRANDIAL**	**HFI** (late-onset forms)	Dumping syndrome
		KETOSIS **AT FAST**		Ketolytic defects Glycogen synthetase deficiency FAODs (SCAD, SCHAD, MCAD) **Ketotic hypoglycaemia** Adrenal disorders GH deficiency /Hypopituitarism Acute liver failure Reye syndrome Intoxication
		HYPOKETOSIS **AT FAST**	**HI/HA**	FAODs Ketogenesis defects GH deficiency/hypopituitarism (early infancy)
		HYPOKETOSIS **POSTPRANDIAL**	**HI/HA** (leucine sensitivity)	
		UNPREDICTABLE		Other forms of hyperinsulinism Factitious

Fig. 3 Diagnostic algorithm to guide the initial approach to hypoglycemia, based on the liver size and the timing of hypoglycemia. Postprandial hypoglycemias of HFI and galactosemias differentiate these disorders from others characterized by fasting or unpredictable hypoglycemias. Hypoglycemias in HI/HA are induced both by fasting and by protein-rich meals (leucine sensitivity). Disorders with similar presenting features are shown as differential diagnosis. Abbreviations: *CDG* congenital defect of glycosylation, *FAODs* fatty acid oxidation defects, *FBPase deficiency* fructose-1,6-bisphospatase deficiency, *HI/HA* hyperinsulinism hyperammonemia syndrome, *MCAD* medium-chain acyl-CoA dehydrogenase deficiency, *SCAD* short-chain acyl-CoA dehydrogenase deficiency, *SCHAD* short-chain 3-hydroxyacyl-CoA dehydrogenase

Disorders triggered by sugars
Case presentation
A female infant was exclusively breastfed until 6 months of age. At 7 months she underwent a normal weaning, but she developed recurrent vomiting. The parents gradually eliminated from her diet several foods, in particular mousse fruits, because the patient seemed to reject them.

At 12 months, the patient had resumed a predominantly milk diet and presented a growth below the 3rd percentile. Her pediatrician suggested biochemical exams and abdominal ultrasound. Blood analyses showed a mild increase of liver enzymes (ALT 98 U/L AST 75 U/L), with normal liver function and no cholestasis.

No sign of malabsorption or gastrointestinal disease was found.

The ultrasonography of the abdomen showed hepatomegaly (the lower margin was 5 cm below the lower pole of the right kidney) and hepatic steatosis.

The patient was brought to the pediatric department of a tertiary care institution for evaluation. Blood exams revealed no significant abnormalities with the exception of hypertransaminasemia (ALT 114 U/L, AST 113 U/L).

The histological analysis of liver biopsy revealed macrovesicular steatosis, mild fibrosis, and no evidence of inflammation, necrosis or bile stasis.
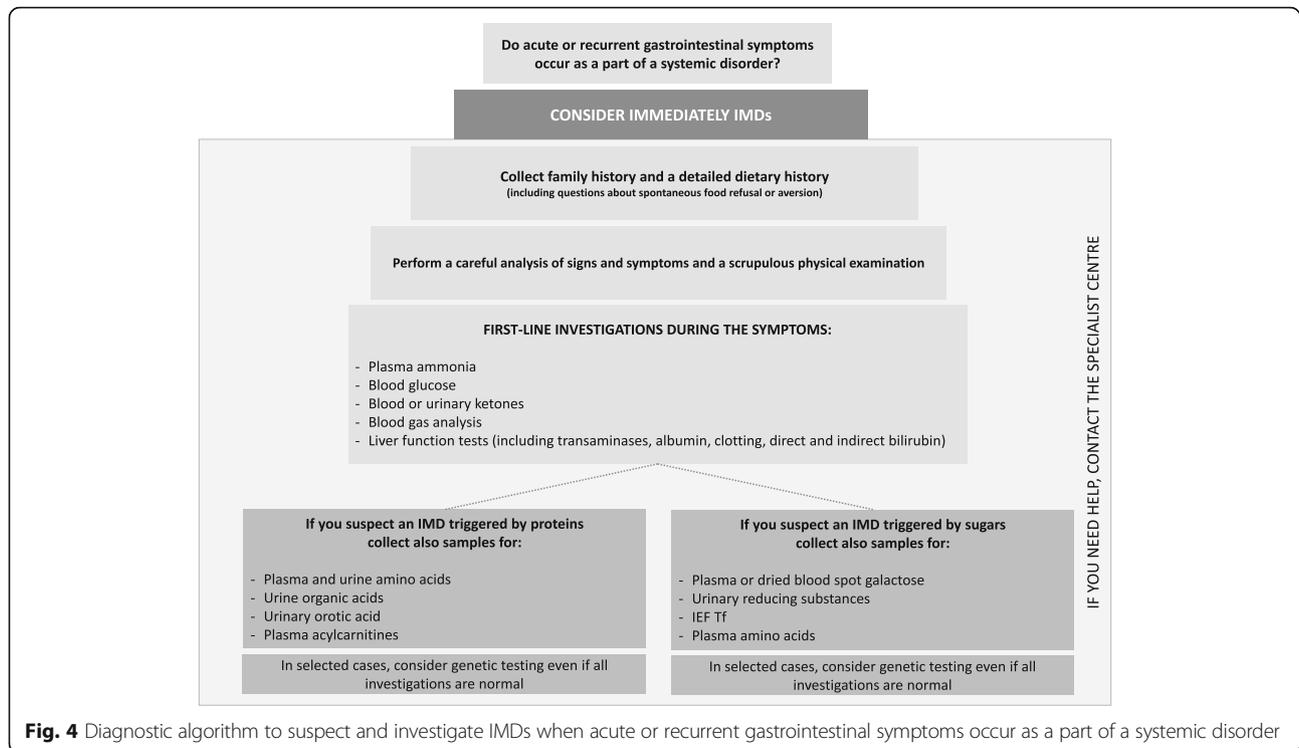
IEF of serum Tf was normal.

Due to the dietary history suggestive for fructosemia, ALDOB gene analysis was performed. The exam revealed the homozygous mutation p.N335 K and confirmed the diagnosis.

A fructose-, sorbitol- and sucrose-free diet was immediately started and there was a complete recovery of the blood abnormalities and a significant reduction of liver size (not published).

Intoxication type disorders triggered by sugars include galactosemia and fructosemia, also known as hereditary fructose intolerance (HFI, OMIM #229600) (Table 2). Intoxication is caused by toxic carbohydrate metabolites derived by exogenous intake of galactose and fructose, respectively [35, 36].

HFI usually presents at the time of weaning, when fruits and vegetables are introduced into the diet. The patients are asymptomatic as long as they avoid foods containing fructose or any of its common precursors such as sucrose (a

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Fig. 4 Diagnostic algorithm to suspect and investigate IMDs when acute or recurrent gastrointestinal symptoms occur as a part of a systemic disorder

disaccharide composed of fructose and glucose, also known as table sugar) and sorbitol (present in natural products, especially in dried fruits, and added to others as sweeteners). Acute symptoms include gastrointestinal discomfort, feeding difficulties, vomiting, pallor, metabolic acidosis, hepatomegaly, hypoglycemia, restlessness, lethargy and shock. Prolonged fructose ingestion can ultimately lead to an aversion towards fructose-containing foods, a strong distaste for sweet food, failure to thrive, liver failure and renal dysfunction [37, 38].

In the case of galactosemia, breastfeeding or lactose-containing formula feeding during the first days of life cause severe liver dysfunction, manifested as jaundice, hepatomegaly, hypoglycemia and coagulation disturbances, and gastrointestinal findings of poor feeding, vomiting and diarrhea. The onset of illness may be acute and fulminant and may often be confused with neonatal sepsis due to the *E. coli* infection [39, 40].

The most prominent features of both defects in acute phase are hypoglycemia and hepatomegaly, even though late-onset forms of HFI may rarely present with isolated hypoglycemia [10].

Postprandial hypoglycemias of HFI and galactosemia differentiate these disorders from others characterized by fasting or unpredictable hypoglycemias (e.g., fatty acid oxidation defects, glycogenosis, hyperinsulinism) (Fig. 3).

HFI is not included in NBS panel, because of technical difficulties in screening for a condition in which there is no neonatal exposure to the offending agent.

On the contrary, most infants with galactosemia are now diagnosed through routine NBS, even if many patients may present symptoms before referral for abnormal NBS. Screening test is done primarily to detect clinically devastating classic galactosemia (CG, OMIM #230400) due to defective function of galactose-1-phosphate-uridyl transferase (GALT) and generalized forms of epimerase deficiency galactosemia (GALE deficiency galactosemia, OMIM #230350), due to defective function of UDP-galactose-4-epimerase (GALE) [39–41].

Conclusions

Despite the introduction of NBS for many IMDs potentially triggered by food intake, pediatricians should systematically consider these disorders in the differential diagnosis of acute or recurrent gastrointestinal symptoms related to food ingestion, in particular if they occur as a part of a systemic disorder.

Once clinical suspicion is aroused, general supportive measures and metabolic laboratory investigations must be undertaken immediately (Fig. 4). Plasma and urine samples should be promptly collected during the acute phase of illness because some tests could be normal during asymptomatic periods.

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IMD(s): Inherited metabolic disorder(s); LDH: Lactic dehydrogenase; LPI: Lysinuric protein intolerance; MSUD: Maple syrup urine disease; NBS: Newborn screening; OA(s): Organic acidemia(s); OTCD: Ornithine transcarbamylase deficiency; Tf: Serum transferrin; UCD(s): Urea cycle disorder(s)

Availability of data and materials
Not applicable

Authors' contributions
ME conceived the work and wrote the draft; DPA revised the manuscript critically for important intellectual content; BA ensured the accuracy of the data and revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Not applicable

Consent for publication
Not applicable

Competing interests
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