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...
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
| 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 |
| 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 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 | Variable. The duration and severity of coma strongly correlate with brain damage |
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 acidaemias (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

| Main presenting biochemical features | IMDs potentially triggered by proteins | Main differential diagnosis |
|--------------------------------------|--------------------------------------|-----------------------------|
| WITH METABOLIC ACIDOSIS              | OA (e.g., MMA, PA, IVA)               | FBPase deficiency*          |
|                                      | MSUD                                 | Glycogen storage disorders (GSD) |
|                                     | [acidosis may be mild or absent in neonatal age and early infancy] | Congenital lactic acidemias (e.g., respiratory chain defects, MCD, PCA) |
|                                     |                                      | Ketotic defects             |
|                                     |                                      | Diabetes                    |
|                                     |                                      | Intoxication                |
|                                     |                                      | Fasting, catabolism, vomiting |
|                                     |                                      | Ketotic hyperinsulinism      |
|                                     |                                      | MCT enriched diet and ketotic diets |
|                                     |                                      | GH deficiency/hypothyroidism|
|                                     |                                      | Adrenal disorders           |
| WITHOUT METABOLIC ACIDOSIS          | MSUD                                 | Glycogen storage disorders (GSD) |
|                                      | [acidosis is usually not severe]      | Congenital lactic acidemias (e.g., respiratory chain defects, MCD, PCA, GAI* |
|                                      |                                      | FADDs (acidosis is usually not severe)* |
|                                      |                                      | Intoxication                |
|                                      |                                      | Renal syndrome              |
|                                      |                                      | Liver failure               |
| WITH METABOLIC ACIDOSIS             | OA (e.g., MIA, PA, IVA)               | FADDs*                      |
|                                      | MSUD                                 |                               |
|                                      | [acidosis may be mild or absent in neonatal age and early infancy] |                               |
| WITHOUT METABOLIC ACIDOSIS          | UCDs                                 | HI/HA*                      |
|                                      |                                      |                               |

* hypoglycemia is usually the main presenting symptom

**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: FADDs fatty acid oxidation defects, FBPase deficiency fructose-1,6-bisphosphatase deficiency, GAI/ glutamic 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, MIMA methylmalonic acidemia, MSUD maple syrup urine disease, OAs organic acidaemias, PA propionic acidemia, PC pyruvate carboxylase, UCDs urea cycle disorders. * hypoglycemia is usually the main presenting symptom.
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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**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 GALT 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. Dypraxias, 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 |
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

| Main presenting features | IMIDs potentially triggered by food | Main differential diagnosis |
|--------------------------|------------------------------------|-----------------------------|
| WITH PERMANENT HEPATOMEGALY | POSTPRANDIAL | CG and GALE HFI |
| AT FAST | | Glycogen storage disorders (Ia, Ib, II, VI, IX) |
| UNPREDICTABLE | | CDG type 1a-1b (due to hyperinsulinism) |
| KETOSIS | POSTPRANDIAL | HFI (late-onset forms) |
| AT FAST | | Ketotic defects |
| HYPOKETOSIS | POSTPRANDIAL | HFI/HA (leucine sensitivity) |
| UNPREDICTABLE | | Other forms of hyperinsulinism |

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, FBPane deficiency fructose-1,6-bisphosphatase 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.
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 hypoglycemics (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.

**Abbreviations**

BCAAs: Branched-chain amino acids; CG: Classic galactosemia; GALE: UDP-galactose-4-epimerase; GALT: Galactose-1-phosphate-uridyl transferase; HFI: Hereditary fructose intolerance or fructosemia; HI/HA: Hyperinsulinism/hyperammonemia syndrome; HP: Erythrophagocytosis; IEF: Isoelectric focusing;
IMD(s): Inherited metabolic disorder(s); LDH: Lactic dehydrogenase; LPl: 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)

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Authors’ contributions

ME conceived the work and wrote the draft; DPA revised the manuscript.

MEC conceived the work, wrote the draft, and made the final revision.

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