

# Pancytopenia –An Uncommon Presentation of an Inborn Error of Metabolism.

## Running Title: Organic acidemias presenting as pancytopenia

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### Abstract

Pancytopenia as a presenting feature of an Inborn Error of Metabolism (IEM) is rare. Two children with pancytopenia mimicking sepsis are presented here. Investigations revealed pancytopenia and metabolic acidosis. Both had previous episodes of encephalopathy. In view of the persisting pancytopenia, episodic encephalopathy and metabolic acidosis, despite therapy for sepsis, an underlying IEM was considered and further workup revealed organic acidemia. Both children were started on dietary modifications and supplements, to which they responded, however one of them succumbed to an intercurrent infection. IEM should be considered in children with episodic encephalopathy, metabolic acidosis and pancytopenia after ruling out sepsis. Timely intervention can reduce morbidity and mortality.

**Keywords:** IEM; pancytopenia; organic acidemias; sepsis; metabolism; carnitine; cytopenias; neurological impairment

### Introduction

Inborn errors of Metabolism (IEM) are rare disorders. Pancytopenia as the presenting feature of an IEM is an uncommon clinical scenario. It is seen in organic acidemias like methyl malonic acidemia, propionic acidemia and isovaleric acidemia. This report describes two children who presented with pancytopenia and features suggestive of sepsis. However evaluation revealed an underlying organic acidemia.

**Case 1:** A 4 year old girl presented with a 3 day history of vomiting and drowsiness. On examination she was lethargic and dehydrated. Rest of the systemic examination was normal. Her initial investigations showed: Hb: 9 mg/dl; Total Leucocyte count: 2000/dL; Differential count: Neutrophils 49%; Lymphocytes 51% ANC: 980; Platelet count: 45,000/uL. Urine culture revealed growth of E coli with colony count of more than 10<sup>5</sup> CFU. An arterial blood gas performed in view of the lethargy showed a pH of 7.2 and bicarbonate of 12mmol/L. Initially a possibility of urinary tract infection with sepsis was considered. The pancytopenia and metabolic acidosis was attributed to be a part of sepsis. She was treated with antibiotics and resuscitated with intravenous fluids. However the pancytopenia and metabolic acidosis persisted even after sepsis cleared.

A review of her history revealed that she had had complaints of episodes of vomiting and lethargy since the age of one. These symptoms recurred every 3 months and would last for 2 to 3 days requiring

hospitalization and intravenous fluids. She had recovered rapidly from these episodes of vomiting and had been asymptomatic in the interim.

In view of episodic vomiting with encephalopathy, persistent metabolic acidosis and pancytopenia, a possibility of an inborn error of metabolism was considered. The metabolic work up revealed the plasma ammonia to be 150 mcmoles/L with positive urine ketones. Blood spot tandem mass spectrometry (TMS) revealed isovaleryl /2 methylbutyrylcarnitine levels of 3.95 micromoles/L. (normal 0.03 -0.65 micromoles) which was suggestive of Isovaleric acidemia, which was further confirmed with urine organic acid estimation. The child was initiated on diet modification and supplements and recovered. Avoidance of fasting, a low protein diet and supplementation of carnitine was initiated. The pancytopenia resolved in a period of 10 days. She has not had any more episodes of vomiting or lethargy and is on follow-up and doing well.

**Case 2:** A one-year old boy presented with fever, fast breathing and lethargy of two days duration. On examination he was in altered sensorium with respiratory distress. His respiratory examination revealed fine crepitations in all lung fields. Initially possibility of bronchopneumonia was considered and he was treated with antibiotics. His initial investigations revealed pancytopenia with metabolic acidosis. Hb: 8g%; Total leucocyte count: 1800 /dL; Differential count: Neutrophils 40%; Lymphocytes 60%; ANC: 720; Platelet counts: 90,000/uL; ABG: PH: 7.1; HCO 3.8. A review of history revealed that in the neonatal period he had been admitted on day 10 of life for suspected sepsis. He had been documented to have pancytopenia with metabolic

acidosis at the time. He had recovered from this episode with therapy for sepsis. The developmental history suggested a global delay in development and he had continued to have seizures in the form of GTCS for which he was on treatment. During this episode also he was noted to have a waxing and waning of sensorium with persisting metabolic acidosis and pancytopenia.

In view of episodic encephalopathy, developmental delay, seizures, metabolic acidosis and pancytopenia, a neuro-metabolic disorder was considered. Metabolic workup revealed plasma NH<sub>3</sub> -250 mcmoles/L and urine ketone +. TMS revealed propionyl carnitine levels of 12.57 micromoles/L (normal 0.3 – 5.8 micromoles/ L) suggestive of propionic acidemia. Urine organic acid levels confirmed it.

With supportive treatment he initially improved symptomatically, blood counts improved in 14 days and he was discharged but was lost to follow up. On contacting the parents it was found that he had developed another episode of alteration in consciousness and fast breathing and had succumbed at another centre.

## Discussion

Pancytopenia may be a subtle clue to underlying IEM. The classical symptom complex in a neonate or young infant of vomiting, hypoglycemia, metabolic acidosis and encephalopathy suggest the possibility of an IEM. A subset of children may not present during the neonatal period, but may present later on, with the intervening period being uneventful. The age of presentation of the IEM depends on the degree of absence of the enzyme in that particular metabolic pathway.

Both Isovaleric acidemia and propionic acidemia present in two distinct forms. The acute neonatal form presents in the first 2 weeks of life. The chronic intermittent form in contrast, presents later in infancy or childhood [1]. The episodes of metabolic decompensation are triggered by infections or increased protein load. It is interesting to note that the resulting pancytopenia can itself further lead to infections. Hence infections can both precipitate or be the result of the metabolic imbalance. Both types of presentations may occur in the same family. While the first child in this report presented late, the second had been treated for “sepsis” and acidosis in the early neonatal period.

The presence of underlying IEM may not be evident at admission unless a careful history of previous clinical symptoms is reviewed. A high index of suspicion is required to keep the possibility of an underlying IEM in mind. In both the presented cases there were significant time periods when the children were asymptomatic. However the recurrence of symptoms of vomiting and altered sensorium and the degree of metabolic acidosis out of proportion to the severity of the presumed “sepsis” were clues in these children, to consider a possibility of IEM.

The findings of metabolic acidosis and pancytopenia in a child often prompt the pediatrician to diagnose and treat sepsis. However, it is important to entertain a possibility of an IEM in such a setting in the differential diagnosis and work-up. The pancytopenia noted in these cases as a consequence of the IEM could further provide a setting for worsening metabolic imbalance because of concomitant sepsis. In the cases presented here the low blood counts persisted even after blood and other body fluid cultures came in negative. Pancytopenia is seen in organic acidemias like propionic acidemia, isovaleric acidemia and methyl malonic acidemia. The incidence of pancytopenia in organic acidemias like propionic acidemia is up to 17 % [2]. The toxic metabolites that accumulate in these diseases have been shown to inhibit the maturation of hematopoietic stem cells, and reduce the RBC life span,

thereby causing pancytopenia [3]. Human serum of an infant with propionic acidemia caused in-vitro suppression in a mouse model of CFU-E and CFU-GM (colony forming unit erythroid and granulocyte-monocyte) [3]. In a case series of 55 patients with propionic acidemia, anemia and pancytopenia were not only found during metabolic decompensation but also in the stable state. In that series anemia was present in 82%, neutropenia in 29% and thrombocytopenia in 35% of patients. Most patients had more than one episode of anemia/ neutropenia [4]. In selected cases GCSF (colony stimulating factors) may be considered if neutropenia is not resolving and there is evidence of bacterial infection with neutropenia.

The hematological manifestations of IEM are varied [5]. Tavil et al studied children with metabolic diseases referred to the pediatric hematology unit for evaluation and found anemia of chronic disease (54%) and nutritional anemia (35%) as most common causes of anemia. In their series 17% of children with IEM presented with pancytopenia / bicytopenia. In a recent series by Kose et al [6], 35% had chronic anemia, 7.1% had pancytopenia and 33.3% had neutropenia. Hematologists would be well advised to keep this in mind as bicytopenia/pancytopenia with infections often prompts workup for inherited bone marrow failure syndromes or primary immune deficiency diseases. IEM may not be considered unless there is a careful assessment of other parameters like blood gas analysis or serum ammonia. Children with the chronic intermittent forms of IEM may have intermittent cytopenias and neurological impairment but most some can have normal growth and development. However death from acidotic episodes can occur at any age. Therefore, an urgent diagnosis and appropriate follow-up is extremely important.

## Conclusion

IEM can mimic sepsis and this can be a diagnostic dilemma to the treating physician. In children who present with episodic or persistent cytopenias, episodic encephalopathy and metabolic acidosis, IEM should be strongly considered in the differential diagnosis. Early diagnosis and introduction of appropriate supplements with dietary modifications can significantly reduce the morbidity and mortality of the disorder.

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