Editorial

Hyperammonemia and inborn errors of metabolism

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Hyperammonemia is an accumulation of ammonia, a nitrogen compound, resulting from protein catabolism, either by intestinal bacteria, or by muscle proteins in the presence of reduced energy sources (1,2). Following its production, ammonia is then coupled with glutamate for glutamine synthesis and later used by hepatic metabolism (urea cycle) to convert it into urea and subsequent excretion by the kidney (3).

With multiple situations that could lead to hyperammonemia in infants and newborns, there is no final consensus on what constitutes normal ammonia values thus far. Commonly used cutoffs are below (healthy) and above (sick) 100 µmol/L (4,5).

Hyperammonemia etiologies have been divided into three groups (4,6,7):

- Primary. Direct dysfunction of urea cycle enzymes
- Secondary. Other related enzymes leading to indirect dysfunction of the urea cycle
- Others. Situations that could lead to increased ammonia production/processing such as liver dysfunction, infections, medications or transient status in the newborn.

Most etiologies within the primary and secondary causes of hyperammonemia correspond to a larger group of conditions known as inherited metabolic disorders (IMD) or inborn errors of metabolism (IEM) (8). These group of disorders could be fatal if not promptly identified.

The symptomatology of hyperammonemia, regardless of etiology, is non-specific. Symptoms such as decreased appetite, dyspnea, hypothermia, lethargy, seizures and ultimately coma (due to cerebral edema) could be seen in most if not all the conditions (according to severity) listed above (8). Therefore, proper diagnostic work-up (blood-urine cultures, cerebrospinal fluid (CSF) analysis, liver synthetic function tests, renal function tests and metabolic tests e.g., plasma acylcarnitines, plasma amino acids, urine organic acids) is essential towards specific and more efficient management (6,9).

As confirmed by Li *et al.* the most common genetic disorders leading to hyperammonemia in their cohort were cholestasis related disorders, urea cycle disorders and organic acidemias (10). The latter two groups are often linked, as organic acids are regulators of essential enzymes such as N-acetylglutamate synthase (11). Another interesting detail is that their most common single gene etiology was citrullinemia type 2/citrin deficiency (*SLC25A13*) a condition that some researchers classify as urea cycle disorder while some others consider it primarily a cholestasis/liver disorder that collaborates with the cycle (12). Citrullinemia type 2 has a large prevalence in Japan, but in the past few years, other East Asian populations like China, have demonstrated a higher prevalence as well, which is further confirmed by Li *et al.* (13,14).

Li *et al.* further solidified that IEMs known to cause hyperammonemia continue to be the most frequent genetic etiologies for this situation. And while they were able to identify other genes not previously associated to hyperammonemia, such as *JAG1*, one must be careful

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upon correlating these data, as there could have been other confounding factors not previously recorded; a limitation clearly stated by the authors.

The impact of understanding the presentation and prevalence of these hyperammonemia related IEMs lies on timely diagnosis. While hyperammonemia could be fairly controlled with either high caloric intake (either through intravenous fluids or orally), nitrogen scavengers (such as sodium benzoate or glycerol phenylbutyrate) or ultimately by continuous renal replacement therapy; there is a high recurrence risk as the main trigger (which in some cases could just be a large meal) has not been identified nor managed (6).

And as we are turning into a rare disease therapeutics era that not only involves organ transplantation for IEMs, but also mRNA and gene therapy, knowing the most relevant details of these conditions will become paramount for their care (15-18).

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