IJN
Iranian Journal of Neonatology
http://ijn.mums.ac.ir

Open Access
Original Article

Diagnosis and Management of Hyperammonemia in Newborns: Is It Still a Challenge?

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ABSTRACT

Background: Hyperammonaemia is a serious cause of mortality and morbidity duringin the neonatal period, regardless of the aetiology. Quickly differentiatingon between inherited metabolic diseases (IMDs) and other causes is important in terms of for treatment and prognosis. We This study aimed to determine the diagnostic and prognostic differences between IMD- and non-IMD-related causes with based on a literature review.

Methods: Clinical and laboratory data of newborns treated for hyperammonaemia between 2016 and 2019 were evaluated retrospectively.

Results: Hyperammonaemia was detected in 60 out of 1963 (3%) patients, and 25% of these patients were diagnosed with IMD. The most common non-IMD etiologies were sepsis (31.6%) and prematurity (31.6%). Significant differences were detected between the two groups inregarding gestational age (P=0.001) and birth weight (P=0.005)were detected (p=0.001 and p=0.005, respectively). Moreover, another significant difference was observed between the two groups in terms of glutamine (P=0.004), alanine (P=0.004), and citrulline (P=0.001) levels and as well as the proportions of glutamine to arginine (G/A)P=0.001), citrulline (G/CP=0.0001), ornithine (G/OP=0.003), and alanine (G/A) (P=0.003).

Conclusion: Metabolic screening tests should be performed to rapidly diagnose hyperammonaemia. In addition to the diagnosing diagnosis of IMDs, it can promptly differentiate non-metabolic causes.

Keywords: Hyperammonemia, Metabolic tests, Newborns

Introduction

Ammonia is an organic metabolite that removes excess nitrogen components during metabolism. In the event of insufficient ammonia excretion, the ammonia concentration increases, leading to toxicity. Normal ammonia levels are < 110 µmol/L (190 µg/dL) in newborns and < 80 µmol/L (140 µg/dL) in infants. Ammonia levels should be examined and treated when they are > 150 µmol/L (260 µg/dL) in neonates and > 100 µmol/L (175 µg/dL) in infants (1).

The maximum level and duration of ammonia elevation are the main factors affecting mortality and morbidity (2). Clinical findings of hyperammonaemia in newborns are normal appearance at birth, lethargy, metabolic coma, loss of thermoregulation ability (hypothermia), difficulty in feeding, neurologic posturing (cerebral edema), seizures, hyperventilation, and hypoventilation (3). Unlike other periods of life, the aetiological factors causing hyperammonaemia have a wide spectrum in the neonatal period.

Inherited metabolic diseases (IMDs) are the fateful causes of hyperammonaemia in the neonatal period. Ammonia elevation due to five enzyme and transport defects that directly affects the urea cycle is called *primary hyperammonaemia,* which constitutes the most important and frequent type (Figure 1) (4-9). *Secondary hyperammonaemia* is caused by increased metabolites due to other enzyme

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Please cite this paper as:
Ersoy M, Salihoglu O, Cetin T. Diagnosis and Management of Hyperammonemia in Newborns: Is It Still a Challenge? Iranian Journal of Neonatology. 2021 Jul: 12(3). DOI: 10.22038/ijn.2021.54350.2001

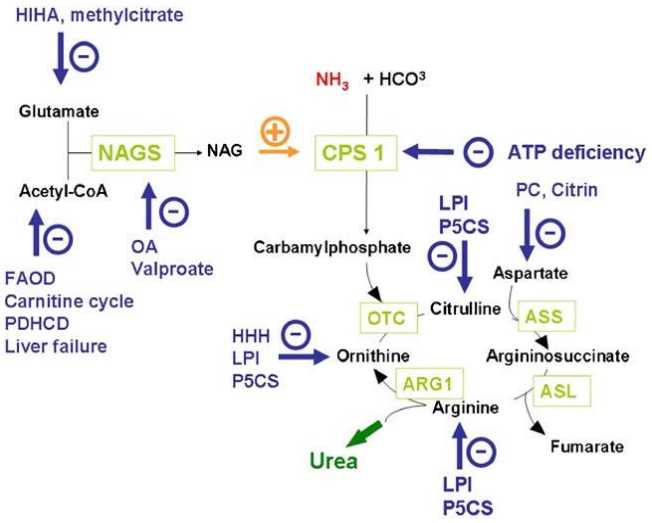

Figure. 1. Primary and secondary causes of hyperammonaemia. This figure is adapted (2).
ARG 1: arginase 1; ASL: argininosuccinate lyase; ASS: argininosuccinate synthetase; CPS 1: carbamoyl phosphate synthetase 1; FAODs: Fatty acid oxidation disorders; HHH: hyperornithinaemia-hyperammonaemia-homocitrullinuria syndrome; HIHA: hyperinsulinism-hyperammonaemia syndrome; LPI: lysinuric protein intolerance; NAG: N-acetylglutamate; NAGS: N-acetylglutamate synthetase; OA: organic acidaemia; OTC: ornithine transcarbamylase; PC: pyruvate carboxylase defect; P5CS: pyrroline-5-carboxylate synthetase defect; PDHCD: pyruvate dehydrogenase complex deficiency; TPN: total parenteral nutrition

defects that inhibit the urea cycle in various ways.

The foremost secondary causes are organic acidaemia and fatty acid oxidation defects (10,11). Medium-chain acyl-CoA dehydrogenation deficiency, multiple acyl-CoA dehydrogenation deficiency (MADD), and defects of the carnitine cycle (e.g., the neonatal form of carnitine palmitoyltransferase II [CPT II]) inhibit the urea cycle by causing acetyl CoA depletion (12,13).

Although rare, hyperammonaemia can also develop due to acquired or inherited defects in glutamine synthetase functioning. Nevertheless, ammonia concentrations due to these defects are generally less common than those due to the primary or secondary causes of hyperammonaemia as ammonia is still removed by the urea cycle (14). Some mitochondrial diseases, such as pyruvate dehydrogenase and pyruvate carboxylase deficiencies, may also lead to a reduction in the energy required to complete the urea cycle (15,16). Lysinuric protein intolerance causes the loss of dibasic amino acids (i.e., arginine, lysine, ornithine) from the kidneys and the intestinal system. It also inhibits the progression of the cycle due to a lack of intermediate metabolites required to complete the urea cycle (17) (Figure. 1).

Besides the primary and secondary causes, some additional states have been identified that lead to high levels of ammonia. Multiple organ failure, acute/chronic liver failure, severe infection, prematurity, asphyxia, congenital shunts or vascular malformations, medications, total parenteral nutrition (TPN), or nutritional carnitine deficiency may cause hyperammonaemia (18-26). It should be noted the treatment protocols for each of these conditions are different.

Transient hyperammonaemia of the newborn (THAN), which is most common in infants with respiratory distress syndrome and preterm infants (GA<37), can also cause serious mortality and morbidity (27). Although the cause is still unknown, some studies have reported that open ductus venosus may be a cause (28). Regardless of the cause, THAN is diagnosed only after excluding the other causes. Sometimes THAN can be caused by IMDs, newly defined carbonic anhydrase VA deficiency, which is a cause of hyperammonaemia, metabolic acidosis, respiratory alkalosis, hypoglycaemia, increased serum lactate and alanine, and impaired provision of bicarbonate to essential mitochondrial enzymes (29). It should be mentioned that THAN is considered to be a benign and transient cause of hyperammonaemia.

Although metabolic tests provide rapid results, they are not always sufficient for the specific diagnosis of hyperammonaemia. Clinical findings and time of onset cannot provide a meaningful outcome prediction and are not practical. This study aimed to determine the etiology, diagnosis, and prediction of prognostic parameters of hyperammonaemia by evaluating the clinical findings and laboratory data of newborns.

Methods

In total, 60 newborns with ammonia levels of > 200 µmol/L who were treated in our newborn

intensive care unit between January 2016 and December 2019 were evaluated retrospectively. Demographic, laboratory, and clinical data were obtained from the electronic record system of the hospital and 60 newborns with available data were included in the study.

Biochemical and metabolic tests (i.e., plasma amino acids, carnitine acylcarnitine profiles, and urine organic acids), as well as advanced genetic tests, were performed. Quantitative determination of amino acids was analyzed by liquid chromatography-mass spectrometry. Moreover, the carnitine/acylcarnitine profile was analyzed using the Tandem mass spectrometry method. In addition, urine organic acid was analyzed by the gas chromatography-mass spectrometry method.

The collected data were analyzed in SPSS for Windows (version 23.0). Categorical variables were determined as frequency and percentage rate, and numerical variables were determined as mean±SD. A group comparison through Student's t-test was used for normally distributed numeric variables, and the Mann-Whitney U test was used for non-normally distributed data. A p-value of less than 0.05 was considered statistically significant.

This study was prepared in accordance with the ethical principles of the World Medical Association Declaration of Helsinki (2000). Moreover, it was approved by the local Ethics Committee of Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey.

Results

Clinical profiles

Hyperammonaemia was detected in 60 out of 1963 (3%) hospitalized patients. It should be mentioned that 53% and 57% of the patients were male and had consanguinity, respectively. The average duration of hospitalization was 22.36±8.48 days. Moreover, 13.3% (n=8) of these patients were referred from other centers for the diagnosis and treatment of hyperammonaemia, while 86.7% (n=52) of them were born in our unit.

The underlying inherited metabolic disease was determined in 15 (25%) cases. When evaluated aetiologically, 76 out of 10,000 total newborns were diagnosed with IMDs, and 36 out of 10,000 newborns born in our center were diagnosed with IMDs. It should be mentioned that seven patients died during the follow-up period. The total mortality rate in hyperammonaemia patients was 11.7%; 5 of the patients who died were in the IMD group, and the mortality rate of IMD-related hyperammonaemia was 33.3%.

Patients diagnosed with IMDs had urea cycle disorder (two with carbamoyl phosphate synthetase deficiency, two with N-acetyl-glutamate synthase (NAGS) deficiency, and two with citrullinemia disorder), fatty acid oxidation disorder (two with CPT II disorder), organic acidaemia (two with methylmalonic acidaemia, one with propionic acidaemia, and one isovaleric acidaemia), and pyruvate dehydrogenase deficiency. One patient was diagnosed with MADD and one patient was diagnosed with Zellweger syndrome. Patients with Zellweger syndrome were included in the IMD group, even though the underlying cause was liver failure (Table 1).

Table 1. Diagnosis of patients

	N (%)
Inherited metabolic disease	15 (25) 2 Carbamoyl phosphate synthetase I deficiency 2 N-acetylglutamate synthase deficiency 2 Citrullinemia type 1 2 Carnitine palmitoyltransferase II deficiency 2 Methylmalonic aciduria 1 Propionic aciduria 1 Isovaleric aciduria 1 Pyruvate dehydrogenase deficiency 1 Multiple acyl-CoA dehydrogenation deficiency 1 Zellweger syndrome
Premature	19 (31.6)
Low birth weight	16 (26.7)
TPN	43 (71.7)
Sepsis	19 (31.6)
Asphyxia	5 (8.3)
Low free carnitine levels	4 (6.7)
Neonatal convulsion (valproic acid)	1 (1.7)
Hepatic hemaengioma and thrombosis	1 (1.7)
THAN	2 (3)

A case can have more than one diagnosis. THAN: transient hyperammonaemia of the newborn, TPN: total parenteral nutrition

Table 2. Demographic and clinical characteristics of patients

	Groups	N	Mean	Std. Deviation	P
Birth weight (kg)	Non-IMD	42	2669.40	752.93	
	IMD	14	3289.64	367.17	0.005
	All	56	2824.46	726.57	
Birth Height (cm)	Non-IMD	21	47.83	3.21	
	IMD	5	50.40	2.51	0.506
	All	26	48.32	3.21	
Head circumtance (cm)	Non-IMD	22	33.13	2.34	
	IMD	4	35.00	1.58	0.514
	All	26	33.42	2.31	
Gestational age (week)	Non-IMD	43	36.19	3.60	
	IMD	14	38.71	0.91	0.001
	All	57	36.81	3.34	
Delivery route	Non-IMD	42	0.40	0.49	
	IMD	13	0.46	0.51	0.578
	All	55	0.42	0.49	
APGAR 1	Non-IMD	27	6.70	2.46	
	IMD	3	6.67	1.52	0.419
	All	30	6.70	2.36	
APGAR 5	Non-IMD	27	8.30	1.77	
	IMD	3	8.00	1.00	0.324
	All	30	8.27	1.70	
Onset of hospitalization (day)	Non-IMD	36	4.28	7.59	
	IMD	10	6.70	7.25	0.981
	All	46	4.80	7.50	

IMD: Inherited metabolic disease

It should be noted that 19 (31.6 %) out of 60 cases were preterm births. Moreover, 16 (26.7 %) patients had low birth weight (<2500 g.), and four had very low birth weight (<1500 g.). Significant differences in gestational age (P=0.001) and birth weight (P=0.005) were detected between the two groups (Table 2). Among the patients without the metabolic disease, six cases were culture-positive and 13 presented with clinical sepsis, accounting for 31.6 % of the total cases. In five patients, only a history of asphyxia was detected without any additional disease.

One of the cases was a patient for whom valproic acid treatment was initiated due to neonatal convulsion. In one case, a 25 mm x 42 mm hepatic haemangioma was detected on abdominal ultrasound while the left hepatic vein was examined for thrombosis. Moderate-type patent ductus arteriosus was detected in two cases while no specific underlying cause could be found in six cases. Moreover, four out of the six patients whose etiology could not be identified were found to have low blood free carnitine levels. During hospitalization, 71.7 % (n=43) of the patients received TPN for various periods (Table 1).

There was no statistically significant difference between the two groups in terms of the route of delivery, height, head circumference, or Apgar scores at the first and fifth min. (Table 3). Emesis, disruption in feeding, hypotonia, and tachypnoea were common findings, and no significant differences were observed between the two groups on the day of onset of clinical findings (P=0.981). There was no statistically significant difference between the two groups regarding the length of hospital stay (Table 3).

It should also be noted that nine patients underwent continuous venovenous haemodia-filtration. High carbohydrate and low-protein diet therapy was initiated and nitrogen scavengers were administered in 48 (80%) of the cases, including 15 (100%) of the IMD and 33 (73%) of the non-IMD cases.

Laboratory profiles

The average maximum ammonia levels were 1788±1521 µmol/L (normal range: 226-4150) in the IMD group and 277±96 µmol/L (normal range: 202-712) in the non-IMD group with a significant difference (P<0.05). Ammonia levels in 13 (21.7%) patients were above 500 µmol/L, 12 of which (92.3%) were in the IMD group. There was no statistically significant difference in the biochemical test results, including urea, in the two groups. Apart from the prediagnosis of metabolic disease, metabolic tests were evaluated to determine differences between the two groups.No significant differences were observed between the two groups in terms of urine organic acid and the carnitine acylcarnitine profile. The plasma amino acid profile was comparatively evaluated in both groups. The mean peak glutamine level was 1346±1197 µmol/L (normal range: 297-3788) in the IMD group and 590±215 µmol/L (normal

Table3. Laboratory findings of patients

	Groups	N	Mean	Std. Deviation	P
Ammonia	Non-IMD	45	277.56	96.11	
	IMD	15	1788.07	1521.32	0.002
	All	60	655.18	595.55	
Glutamine 295-900*	Non-IMD	24	590.37	215.91	
	IMD	14	1346.14	1197.68	0.004
	All	48	868.81	818.21	
Alanine 150-520*	Non-IMD	24	410.50	179.88	
	IMD	14	1036.28	1630.49	0.004
	All	48	641.05	1023.61	
Arginine 16-140*	Non-IMD	24	65.45	38.79	
	IMD	14	68.14	64.77	0.574
	All	48	66.44	49.10	
Ornithine 30-140*	Non-IMD	24	110.83	76.72	
	IMD	14	120.07	68.54	0.750
	All	48	114.23	73.01	
Citrulline 9-44*	Non-IMD	24	13.16	5.77	
	IMD	14	274.71	719.95	0.001
	All	48	109.52	445.51	
Urea	Non-IMD	35	17.42	9.72	
	IMD	14	14.28	21.02	0.095
	All	49	16.53	13.74	
Glutamine/Ammonia	Non-IMD	24	0.89	0.38	
	IMD	14	2.33	1.04	0.001
	All	48	1.80	1.11	
Glutamine/Arginine	Non-IMD	24	11.29	5.95	
	IMD	14	27.88	28.04	0.001
	All	48	17.40	19.08	
Glutamine/Citrulline	Non-IMD	24	49.87	24.15	
	IMD	14	574.40	1079.37	0.0001
	All	48	256.50	710.61	
Glutamine/Ornithine	Non-IMD	24	7.41	4.78	
	IMD	14	13.57	12.10	0.003
	All	48	9.68	8.64	
Glutamine/Alanine	Non-IMD	24	1.52	0.43	
	IMD	14	2.76	4.36	0.003
	All	48	1.98	2.67	

*µmol/L; IMD: Inherited metabolic disease

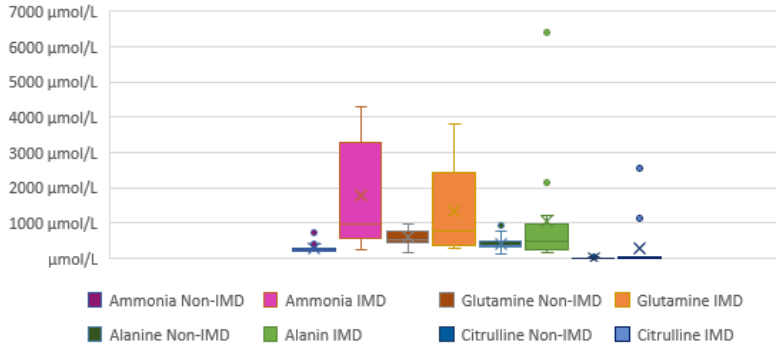

Figure 2. Ammonia, citrulline, alanine, and glutamine levels of IMD and non-IMD groups

range: 180-980) in the non-IMD group.

Significant differences were observed between the two groups regarding glutamine (P=0.004), alanine (P=0.004), and citrulline (P=0.001) levels (Figure 2). Moreover, there were significant differences between the two groups regarding the proportions of glutamine to arginine (P=0.001) and citrulline (P=0.0001) and moderately

significant differences in the proportions of glutamine to ornithine (P=0.003) and alanine (P=0.003) (Table 3).

Discussion

Hyperammonaemia is a metabolic emergency in newborns due to its high mortality and morbidity. Its incidence rate in newborns is unknown due to delays in diagnosis and evaluation. Most case series studies have examined the inherited metabolic causes of hyperammonaemia. Many of the created diagnosis and treatment algorithms do not consider other causes. In this study, hyperammonaemia and IMD were detected in 3% and 25% of the patients. In the total population, 76 out of 10,000 and in the neonates born in our center, 36 out of 10,000 were diagnosed with IMDs, respectively. This rate is consistent with those reported in the literature (30,31).

Despite several advanced methods for its diagnosis and treatment, death still occurs in one-third of all cases.(5) The two most important conditions that determine mortality and morbidity are the peak concentration and duration of elevated ammonia. In addition, it seems that the underlying etiology in newborns has an impact on prognosis since ammonia values above 500 µmol/L were observed in those with IMDs (32). In the present research, it was determined that 92.3% of the patients whose ammonia was above 500 µmol/L had IMDs. An important reason for the high mortality rate among the IMD group (33.3%) in this study seems to be the delayed diagnosis of hyperammonaemia in patients referred from other centers, the prolonged referral time, and the development of irreversible clinical findings.

A high rate, i.e., three-quarters, of hyperammonaemia developed due to non-metabolic and mostly transient causes. Prematurity (31.6%) and neonatal sepsis (31.6%) were the two most common non-IMD causes of hyperammonaemia. Physiologically, these two conditions cause increased ammonia production and/or impairment of ammonia detoxification (2,20,21,33). Infections due to urease-producing microorganisms (some Proteus and Klebsiella species) can increase ammonia production in the urinary tract or intestine (20,21). The most common microorganisms in our cases with infection were methicillin-resistant coagulase-negative staphylococci and enterococci. In these cases, the ammonia level returned to the normal range within days (34,35,36).

Persistent portosystemic shunt, enzyme immaturity, TPN, high risk of sepsis, and low levels of essential amino acids and free carnitine increase the risk of hyperammonaemia in premature neonates.(37) It has been shown that asphyxia can cause hyperammonaemia, especially in preterm infants, by causing catabolism (22). In the present study, asphyxia was the only etiology detected in 8.5% of the patients. Despite its frequency in preterm infants, nutritional carnitine deficiency leads to acetyl CoA deficiency which, in turn, leads to impaired fatty acid oxidation (23,24). A lack of arginine in TPN preparations may cause a lack of intermediate substrates, leading to hyperammonaemia (25). In total, 71.7% of the patients received TPN, but it was not determined whether it played a role in the etiology. Therefore, it can be said that there is a need for further comparative studies.

Congenital portosystemic shunts and vascular malformations that cause the direct attachment of the portal system to the inferior vena cava can cause mild to moderate hyperammonemia (26,38). Shunts sometimes close spontaneously over time, but surgical operation may be required (39). To avoid missing the diagnosis, echocardiography and abdominal ultrasound were performed to identify patent ductus arteriosus and vascular malformations, respectively. After treatment for liver haemangioma, it was observed that the ammonia level in our patients decreased to the normal range within hours.

It must be noted that medicines can also cause hyperammonaemia. In newborns receiving valproic acid treatment for epilepsy, hyperammonaemia can occur due to both NAGS inhibition and carnitine depletion (23). Antiepileptic, antibiotic, and chemotherapeutic medications that can cause liver toxicity have also been found to be causative agents.

Demographic characteristics, time of onset, and the course of clinical findings do not provide clues regarding the diagnosis and prognosis. Therefore, metabolic tests and other imaging examinations should be performed on each patient with an ammonia concentration above 200 µmol/L. Despite the fact that low birth weight and prematurity have been shown to cause temporary increases in ammonia, it is necessary to determine whether there is an underlying IMD.

Biochemical tests did not yield any significant findings for early diagnosis; however, they can indicate organ dysfunction. Metabolic tests can help diagnose organic acidemia, fatty acid oxidation defects, and some urea cycle defects.

Moreover, they can produce results within 24 h;

hence, these tests should be performed on suspected cases. As seen in four of our cases, in patients with carnitine deficiency, ammonia co-concentration can be reduced to the normal range with simple carnitine replacement therapy after evaluation of the carnitine acylcarnitine profile.

Although it cannot indicate specific diagnoses, evaluation of the plasma amino acid profile has been shown to be predictive of IMD and non-IMD diagnoses. In previous studies, even though there was no significant increase in glutamine levels, the plasma glutamine/ammonia ratio was observed to be < 1.6 in patients with THAN (40). Similarly, in the present study, the mean plasma glutamine/ammonia ratio was 2.33±1.04 in the IMD group and 0.89±0.38 in the non-IMD group, which was under 1.6.

Ammonia is detoxified by changing glutamine synthetase to glutamine and also glutamate dehydrogenase and aminotransferase to alanine. Notably, in this study, the mean plasma alanine level and glutamine/alanine ratio in the IMD group were statistically significant. This situation may be associated with higher levels of both ammonia and glutamine in the IMD group, compared to the non-IMD group.

We analyzed the concentrations of intermediate amino acids of the urea cycle, including arginine, ornithine, and citrulline, in plasma and their glutamine ratios. A significant difference was observed between the IMD and non-IMD groups in terms of quantitative levels of glutamine, alanine, and citrulline, and significant differences were observed in the proportions of glutamine to arginine, citrulline, ornithine, and alanine.

Metabolic tests can indicate the need for further evaluation and treatment in hyperammonaemia patients, distinguish between IMD and non-IMD etiologies, and diagnose specific IMDs. Since the prognosis of hyperammonaemias due to non-IMD causes is better, early detection of IMD and non-IMD causes provide a prediction about the prognosis. Consequently, in the present study, the diagnostic and prognostic differences between IMD- and non-IMD-related causes were determined based on a literature review through a comparison of the clinical and laboratory variables between these two groups.

Conclusion

It has been stated that hyperammonemia due to IMDs with high ammonia values is an indicator of a known poor prognosis. In addition to administering rescue therapies, it has been pointed out that metabolic tests may provide secondary findings for the determination of the underlying etiology of hyperammonemia in the neonatal period. In this way, rapid diagnosis and proper treatments can be initiated. To the best of our knowledge, there has been no previous study on the use of metabolic tests in non-IMD hyperammonemia.

Acknowledgments

None.

Conflicts of interest

The authors declare that there were no conflicts of interest in this study.

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