BRIEF COMMUNICATION
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A Study on the Humoral and Complement Immune System of Patients with Organic Acidemia

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ABSTRACT

Patients with organic acidemia are prone to different infections, which lead to acidosis episodes. Some studies have evaluated the status of immune system in acidotic phase in these patients, but to the best of our knowledge no study has evaluated the immune system in non-acidotic phase of the disease.

In this study, thirty-one patients with organic acidemia were enrolled. For evaluation of humoral immunity, serum IgA, IgG, IgE, IgM, isohemaggltuinin titer, anti tetanus and anti diphtheria IgG were measured. For screening of complement deficiencies, serum C3, C4, and CH50 were assessed.

Eleven patients had Maple Syrup Urine Disease (MSUD), 10 had methylmalonic acidemia, 5 had isovaleric acidemia, 4 had glutaric aciduria, and 1 had propionic acidemia. Serum IgM level was less than normal in 2 patients. Serum isohemagglutinin titer was less than 1:8 in 2 other patients. IgA, IgE, and IgG were within normal range for all patients. Anti tetanus and anti diphtheria IgG levels were low in two patients with MSUD. No significant relationship was found between any of the measured parameters and history of recurrent admissions, recurrent infections and the type of their diseases. Five patients had high C3 level, 4 had high C4 level, and 5 had high CH50 percentage. Totally, 10 patients had high complement level, but no remarkable connection was noted between the type of the disease and complement level.

Minor insignificant deficiencies in humoral immunity in non-acidotic phase of organic acidemia were found. Some components of complement system showed increase in some patients, which might be due to decreased pH in extracellular fluid.

Keywords: Immunodeficiency; Metabolic disease; Organic acidemia

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INTRODUCTION

Organic acidemia is a group of metabolic disorders, with disrupted aminoacid metabolism leading to accumulation of aminoacids in the body fluids, which are usually not present.[1] The four main types of organic acidemia are: methylmalonic acidemia, propionic acidemia, isovaleric acidemia, and maple syrup urine disease.[1] Most patients with organic acidemias represent during the newborn period or early infancy. After an initial period of well-being, these patients develop life-threatening episodes of metabolic acidosis characterized by an increased anion gap.[1,2]

A strong association has been postulated between organic acidemia and immunodeficiencies.[1] These patients are prone to develop different infections, leading to acidosis episodes. Some studies have evaluated the status of immune system in acidotic phase in these patients,[3,4] but to the best of our knowledge no study has assessed the immune system in non-acidotic phase of the disease. As in many cases, primary infection results in acidosis attacks with high morbidity and mortality, this study was designed to evaluate humoral and complement parts of the immune system in non-acidotic phase of the disease.

MATERIALS AND METHODS

Thirty-one patients with organic academia, who were referred to Mofid Children Hospital in Tehran, and diagnosed by detection of organic acids in their body fluids, were included in this study. Our patients were in non-acidotic phase of their disease. The patients with acute infections, concomitant chronic diseases, or who were receiving corticosteroids or the other immunosuppresive drugs, were excluded from the study.

After obtaining the informed consent, a complete questionnaire was filled for every patient. Then 5 ml blood was taken from the patients by venipuncture. After separation, the sera were stored at -20° C until the time of performing the tests.

For evaluation of humoral immune system, serum IgA, IgG, IgE, IgM, isohemaggltuinin titer, anti tetanus IgG, and anti diphtheria IgG were measured. For screening of complement deficiencies, serum C3, C4, and CH50 were assessed. IgA, IgG, IgM, C3, and C4 were measured by nephelometry using Binding site kits (Birmingham, UK).

Enzyme-linked immunosorbent assay (ELISA) was used for measurement of serum IgE (Euroimmun kit, Lubeck, Germany), serum anti tetanus and anti diphtheria IgG (Binding site, Birmingham, UK). CH50 percentage was assessed using an immunoenzymatic colorimetric method (Diametra, Spello, Italy).

Isohemagglutinin titer was evaluated by hemagglutination method and titers more than 1:8 were considered normal. All the data were compared with normal ranges for the age range.

RESULTS

Among 31 patients with organic acidemia, 14 (45.2%) were male and 17 (54.8%) were female.The mean and standard deviation of age of the patients were 48.7±35.7 months. Eleven patients had Maple Syrup Urine Disease (MSUD), 10 patients had methylmalonic acidemia, 5 had isovaleric acidemia, 4 had glutaric aciduria, and 1 had propionic acidemia. Among these patients, 54.8% had history of recurrent admission and 41.9% suffered from recurrent infections. The patients' age, sex, type of organic acidemia and the value of measured parameters are summarized in table 1. Each measured parameter was compared with normal range in the same age.

Serum IgM level was less than normal for their age in 2 patients (6.5%). Serum isohemagglutinin titer was less than 1:8 titer in 2 other patients, both of whom were under two years old. Other immunoglobulins (IgA, IgE, and IgG) were within normal range for all patients. Anti tetanus IgG and anti diphtheria IgG levels were very low in two patients with MSUD, despite receiving appropriate vaccinations. However, no significant relationship was seen between immunoglobulins, anti diphtheria and anti tetanus IgG levels and isohemagglutinin titer with history of recurrent admissions, recurrent infections and the type of their disease. None of the patients had complement deficiency, in contrast 5 patients (16.2%) had high C3 level, 4 patients (12.9%) had high C4 level, and 5 patients (16.2%) had high CH50 percentage. Totally, 10 patients (32.2%) had high complement level, but no considerable association was noted between the type of the disease and complement level.

Table 1. The full description of patients'age, sex, type of metabolic acidemia and measured parameters.

Patients' No	Sex	Age (months)	Type of organic acidemia	Blood group	Anti B (titer)	Anti A (titer)	Anti tetanus IgG	Anti diphtheria IgG	IgM	IgA	IgG	IgE	C3	C4	CH50
1	F	52	MMA	O+	>1/64	>1/64	0.97	0.53	271.1	65.2	1040	37	159.2	24.6	100
2	M	45	MSUD	A+	1/32	NA	3.5	>1	103.6	258.2	1243	342	180	35.5	115
3	M	60	IVA	A+	>1/64	NA	0.99	0.6	159.9	242.7	1532	34	203.1	46.6	236
4	F	83	IVA	A+	>1/64	NA	>5	>1	243.1	155.9	1381	0.1	414.6	72.5	228
5	F	17	MSUD	A-	1/32	NA	0.04	0.03	56.8	79.4	728.1	3	180	24.4	100
6	M	102	IVA	O+	>1/64	1/64	0.65	0.79	113.4	156.4	2061	21	170.3	46.9	145
7	M	41	MMA	B+	NA	1/64	4.6	>1	81.5	166.1	957.8	106	143.4	51.6	100
8	F	60	MSUD	O+	>1/64	1/32	0.98	0.89	121.2	49.3	829.9	0.1	175	29	111
9	M	9	MMA	A+	1/64	NA	2	0.6	120.4	33.1	544.7	38	169.1	31	134
10	M	13	MMA	O+	1/32	1/16	1.46	0.77	160.8	37.4	741.3	46	148.2	29.6	100
11	F	37	MMA	O+	1/32	1/64	1.8	>1	276.5	83.5	1137	81	142.1	13.9	106
12	F	4	MSUD	A+	<1/2	<1/2	0.2	0.44	30.7	17	250	0.1	144.1	26.7	250
13	M	24	PA	O+	>1/64	>1/64	>5	>1	136.7	82.4	724.8	6	176	40.3	100
14	M	30	IVA	A+	1/32	NA	>5	>1	61	27.9	1341	0.1	179	37.6	100
15	M	19	MMA	A+	1/16	NA	0.74	>1	51.9	94.4	1335	1045	271.2	40.1	121
16	M	144	MMA	A+	1/32	NA	1.29	0.5	139.2	114.9	1337	442	137.8	33.7	111
17	F	21	MSUD	A+	1/64	NA	0.03	0.02	148.5	95.5	797.5	13	126.6	26	150
18	M	12	MSUD	B+	NA	1/16	4.4	0.96	<18	76.6	870.7	3	356.5	91.3	111
19	F	66	MSUD	O+	1/16	1/64	0.85	0.58	119.1	67.6	934.3	53	153	25.9	251
20	F	75	MMA	B+	NA	1/64	2.3	>1	182.1	185.7	1391	0.2	220.5	38.4	138
21	M	51	MSUD	O+	1/64	1/64	>5	>1	178.1	337.7	1337	30	130.7	19.1	120
22	F	84	MSUD	A+	1/32	NA	>5	>1	79.3	39	1254	48	166.3	26.4	100
23	F	46	MMA	A-	1/32	NA	1.13	0.47	124.7	42.4	1029	2	123.7	24.4	127
24	F	15	IVA	B+	NA	1/16	0.63	0.21	101.8	24.7	1092	42	153.5	22.5	103
25	M	90	MMA	O+	>1/64	1/32	2.7	>1	152.5	292.1	1749	19	120.3	19.8	112
26	F	9	GA	O+	¼	1/4	3.4	>1	110.3	24.2	835.1	9	99.9	29.5	160
27	M	49	MSUD	B+	NA	1/64	3.5	>1	237.5	120.4	1327	235	140.2	17.9	118
28	F	30	GA	A+	1/16	NA	>5	>1	62.9	40.9	997.9	71	122	30.6	108
29	F	42	MSUD	A+	1/16	NA	1.56	0.64	48.5	111.1	1109	1	120.9	14.1	101
30	F	144	GA	AB+	NA	NA	1.14	0.86	64.6	138.7	1513	0.1	173	18.5	100
31	F	36	GA	AB+	NA	NA	0.93	0.46	168.8	66	991	0.1	150.2	16.6	112

IVA: Isovaleric acidemia, GA: Glutaric acidemia, MMA: Methylmalonil acidemia, MSUD: Maple syrup urine disease, NA: Not applicable, PA: Propionic acidemia,

DISCUSSION

Patients with organic acidemia suffer from recurrent infections, which have high morbidity and mortality. Some researchers have reported patients with organic acidemia and recurrent or unusual infections,[5,6] but the association between organic acidemia and immunodeficiencies has not been studied adequately.

Despite finding some deficiencies in this study's patients, we could not find a significant association between evaluated parameters and history of recurrent admissions, recurrent infections and the type of their disease. Although there are some reports on immune system deficiencies during acidosis, but sampling from the patients was done in a not-acidotic phase of their disease.

Raby et al. in 1994 reported that decreased serum IgM, IgG and reduced number of B lymphocytes in acidotic phase of propionic acidemia.[3] The study by Church et al. on patients with methylmaonil acidemia showed reduced number of B and T lymphocytes, decreased serum IgG level and impaired chemotaxis.[4]

The evaluation of immune system in these studies was done in acidotic phase of the disease. Accumulation of organic acids in body fluids may be toxic for components of immune system and in this case good control of the disease can results in better function of immune system and prevention of recurrent infections.

Although statistically insignificant, some minor deficiencies in different components like reduced IgM in 2 patients and impaired response to diphtheria and tetanus vaccine in 2 other patients were found. Immune deficiencies are probable in these patients and more patients should be evaluated to conclude precisely.These patients are currently being studied cellular and phagocytic parts of immune system to have a complete assessment of immunodeficiencies in patients with organic acidemia.

In contrast to normal or slightly decreased humoral immunity, these patients showed normal or high levels of some of complement components. It has been shown that decreased extracellular PH can enhance complement activation and production of some complement components.[7]

Compared to normal subjects, patients with organic acidemia have higher morbidity and mortality during infections. Good knowledge of probable defects in immune system can lead to administration of suitable broad spectrum antibiotics to reduce morbidity and mortality.

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