Clinical and Nutritional Evolution of 24 Patients with Glutaric Aciduria Type 1 in Follow-up at a Center Specialized in Inborn Errors of Metabolism in Chile

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Abstract

INTRODUCTION: Glutaric Aciduria Type 1 (GA-1) is produced by the enzymatic deficiency of glutaryl-CoA-dehydrogenase (GCDH), leading to the accumulation of glutaric acid (GA). 90% of patients without early treatment present acute encephalopathic crisis (AEC), followed by disabling neurological symptoms. The treatment consists of a low lysine (Lys) diet, protein substitute lys-free, tryptophan-reduced (PS) and L-carnitine. OBJECTIVES: Describe the clinical and nutritional evolution of a cohort of GA-1 patients at a national referral center in Chile. METHODOLOGY: Retrospective study of 24 patients diagnosed with GA-1 between 1998-2020 and referred to the Institute of Nutrition and Food Technology (INTA) of University of Chile. RESULTS Age at diagnosis was 19±27 months; 10/24 presented AEC and neurological sequelae. The cases without AEC (14/24) 8 presented neurological compromise: psychomotor development delay, abnormal movements and pyramidal syndrome. Nutritional evaluation: 12/24 were malnourished by deficiency, <6 years old group (12/24): 11 cases were found to have Lys and PS, ≥6 years old (12/24): 9/12 did not receive PS. All had normal free carnitine levels. CONCLUSION: GA-1 has variable symptoms with neurological involvement AEC or insidious start. Is essential to maintain a long-term follow-up and consider its inclusion in neonatal screening programs.

Keywords: Glutaric aciduria type I, encephalopathic crisis, macrocephaly, lysine.

Introduction

GA-I is a neurometabolic disease caused by the deficiency of the enzyme glutaryl-CoA-dehydrogenase (GCDH), which breaks down the amino acids lysine, hydroxylysine and tryptophan. This deficiency produces accumulation of: GA, 3-hydroxyglutaric acid (3-OH-GA), glutaconic acid and glutarylcarnitine acid (C5DC). It is of autosomal recessive inheritance, the enzyme is encoded in the GCDH gene located on chromosome 19p13.2 and more than 200 mutations have been identified [1]. The prevalence is 1:110,000 live births [2].

The diagnosis is made by tandem mass spectrometry to determine levels of C5DC by acylcarnitine analysis and confirmed by urine organic acids analysis [3,4]. The most prevalent are macrocephaly, frontal bossing, delayed psychomotor development and muscle hypotonia [5,6,7]. While findings in neuroimaging tend to be usual for frontotemporal atrophy and subdural hematoma. [8,9,10]

Without treatment, 80-90% of patients show acute encephalopathic crisis in early infancy [6,7] triggered by catabolic stress, such as infections, vaccination, surgery or prolonged fasting. This can occur between 3 and 36 months of age, although there are cases reported up to 72 months, a critical period in which there is greater brain development. After acute encephalopathic crisis (AEC), patients evolve mainly with sequelae such as abnormal movements, dystonic mostly due to selective injury to the striatum, which can lead to acute striatal necrosis [8].

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In 10-20% of cases, they have an insidious start, that is, despite not having had AEC, they present progressive neurological symptoms, with striatal damage demonstrated by neuroimaging, abnormal movements, and hypotonia [11]. Late start presentation is described when the diagnosis is made after 6 years of age, these can present with nonspecific symptoms, predominantly changes in the white matter, headache or diagnosis of maternal glutaric aciduria due to findings in neonatal screening [12,13]. early initiation of nutritional treatment has been shown to be effective in reducing neurological disability and encephalopathic crisis [14,15]. This consists of a low-lys diet, consumption of PS and L-carnitine supplementation [16,17]. Scientific evidence has not reported cases of AEC after the age of 6, so in recent consensuses it is recommended to suspend the intake of PS, to give an intake of protein of high biological value according to the safe levels of intake recommended by the FAO / WHO, maintain a low-lys diet and supplementation with L-carnitine [8]. Emergency treatment should be considered at all times when faced with episodes of catabolic stress, the recommendation is to decrease or suspend intact proteins, double the dose of L-carnitine and increase the caloric intake [18,19].

The objective of this study is to characterize the clinical and nutritional evolution of 24 Chilean patients with GA-1 under active follow-up at the Genetics and Metabolic Diseases Laboratory of the Institute of Nutrition and Food Technology (INTA), Dr. Fernando Monckeberg, Universidad de Chile.

Methodology

Study Design: It is a retrospective study, in which 46 electronic and/or physical records of patients diagnosed between 1998 and 2020 were reviewed. In the 9 deceased patients, we have not all the records available, but 1 died of acute renal failure and 4 for sepsis. All of them presented with AEC and developed severe neurological compromise and undernutrition. Twenty-four cases were selected that met the inclusion criteria: confirmed diagnosis and active follow-up at INTA (≥ 2 medical-nutritional control in the last 3 years).

Background of the Subjects: Admission data such as age at diagnosis, clinical picture at diagnosis, age of AEC, catabolic stress prior to the crisis, age of treatment initiation and neurological sequelae were obtained.

Neurological Evolution: The study group was divided into two groups according to diagnosis and clinical evolution. Group 1: cases with AEC and neurological sequelae; Group 2: cases without AEC and with or without neurological sequelae.

Anthropometric Evaluation: Height and weight measured during control were collected to determine the indicators: weight for age (W/A), weight for height (W/H) and height for age (H/A) for patients <5 years, body mass index (BMI) for age (BMI/A) and height for age (H/A) for patients aged 5 to 19. The z-score for each indicator was calculated to classify nutritional status according to WHO references in 2006 and 2007 by age and sex [20,21].

Nutritional Intake: Of the 24-hour dietary recall recorded, the intake of energy, protein from PS and intact, Lys, L-carnitine, iron, calcium and zinc were analyzed. A differentiation was made between children aged < 6, in which energy intake, PS, Lys (intact protein and/or diet) and L-carnitine were compared with international recommendations (8) and those children aged ≥ 6 according to protein and energy requirements determined by FAO/WHO/UN according to age [22,23]. and L-carnitine according to international protocol (8). Calcium, zinc and iron intakes were all compared according to the recommended daily intake (RDI) and it was considered adequate requirement between 90-110% [24,25].

Level in plasma: The last free carnitine plasma levels (FC), esterified carnitine (EC) and total carnitine (TC) were recorded, considering them as reference values for: FC 19-35 μmol/L, EC 4-14 μmol/L and TC 36-56 μmol/L. These values were determined according to our laboratory for the Chilean healthy population, but not for glutaric patients. Then, it is requested that free carnitine be kept within the normal standardized range, according to international protocols [8].

Informed Consent (IC): Parents or legal guardians signed the IC for the review of physical and/or electronic records of the selected subjects, which was approved by INTA's Ethics Committee in compliance with the Declaration of Helsinki.

Statistics: For the descriptive statistical analysis, the STATA 15.1 software was used, the data are shown as average ± standard deviation.

Results

Sample GA-1 study: Of 24 cases: 15 were boys and 9 were girls, with current ages of 86 ±60 months (range: 8 - 211 months). The diagnostic age was 18±27 months (range: 0.5 - 131 months), 1 case was diagnosed through the expanded neonatal screening pilot program. Regarding diagnostic confirmation: 6/24 had a normal measurement of the C5DC metabolite in the first initial sample, 4 of them showed elevation of C5DC after L-carnitine loading. Regarding the clinical characteristics: 1/24 cases had a history of consanguinity, 10/24 cases presented with AEC (8±3 months old), of these, 8 were associated with infectious conditions, and the diagnosis was made at an average of 24±38 months of age (Table 1A). 14/24 who did not have AEC were diagnosed at an average of 14±17 months of age. Of these, 8 cases had an insidious start with neurological sequelae and 6 had normal development (2 cases diagnosed in the neonatal period by family history of GA-1) (Table 1B).

Clinical manifestations prior to diagnosis: In the clinical picture prior to diagnosis, 21 patients presented macrocephaly (88%), 10 delayed psychomotor development (42%), 10 abnormal movements (42%) and 8 frontal bossing (33%).

Neurological Evolution During Monitoring: Of the group with AEC, all subjects manifested post-diagnosis neurological sequelae: dystonia, pyramidal syndrome, swallowing disorders

Table 1B. Clinical Characteristics GA-1 with AEC (Group 1) prior to diagnosis.

Cases	Sex	Age of Dx (month)	Type of Dx	Pre Dx Catabolism	Age of AEC (months)	CS pre Dx	C5DC	OAU
1	M	6	AEC	Infection	12	Macrocephaly, FB, AM	E	E
2	M	15	AEC	Infection	15	Macrocephaly	N	E
3	F	7	AEC	Surgery	6	Macrocephaly	E	E
4	M	21	AEC	Infection	10	Macrocephaly, DPD, AM	E	E
5	M	15	AEC	Infection	7	Macrocephaly, AM	N*	E
6	F	8	AEC	Infection	8	Macrocephaly, AM	E	E
7	F	131	AEC	Infection	10	Asymptomatic	NR	E
8	F	6	AEC	Infection	6	Macrocephaly, DPD	N*	E
9	M	9	AEC	Infection	9	Macrocephaly, AM	N	E
10	M	24	AEC	Surgery	5	Macrocephaly	N*	E

M: Male, F: Female, Dx: Diagnosis, AEC: Acute Encephalopathic Crisis, CS: Clinical Symptoms, FB: Frontal bossing, AM: Abnormal movements, DPD: Delayed psychomotor development, C5DC: Glutaryl Carnitine, N: Normal, N*: First sample normal, second altered post-load with L-carnitine. E: elevated, NR: not reported, OAU: urine organic acids.

Table 1B. Clinical characteristics GA-1 prior to diagnosis insidious onset group (Group 2).

Case	Sex:	Age of Dx (month)	Type of Dx	CSx at Dx	C5DC	OAU
11	M	49	Clinical	DPD, AM	E	E
12	F	17	Clinical	Macrocephaly, FB, DPD, AM	E	E
13	F	15	Clinical	Macrocephaly, FB, DPD, AM	E	E
14	M	6	Clinical	Macrocephaly, FB, DPD	E	E
15	F	0.6	ENS	Macrocephaly, DPD	E	E
16	F	8	Clinical	Macrocephaly, DPD	E	E
17	M	7	Clinical	Macrocephaly, DPD	E	E
18	M	34	Clinical	FB, DPD, AM	E	E
19	M	3	Clinical	Macrocephaly, DPD	E	E
20	M	48	Clinical	Macrocephaly	E	E
21	M	1	Clinical	Macrocephaly	E	E
22	M	8	Clinical	Macrocephaly, DPD, AM	N*	E
23	M	0.5	ENS	Macrocephaly, DPD	E	E
24	F	6	Clinical	Macrocephaly, mild hypotonia	E	E

M: Male, F: Female, Dx: Diagnosis, ENS: Extended Neonatal Screening, FB: Frontal bossing, DPD: Delayed Psychomotor Development, AM: Abnormal Movements, C5DC: Glutaryl Carnitine, OAU: urine organic acids, E: Elevated, N*: First Sample Normal, Second Altered Post L-Carnitine Load.

and severe psychomotor development delay and/or regression. In the insidious-start group, 8/14 presented neurological sequelae, 8 delay and/or regression of psychomotor development, 7 abnormal movements, 2 pyramidal syndrome and 2 swallowing disorders (Table 2).

Evaluation of the nutritional state: Of a total of 24 patients, it can be observed that 12 presented malnutrition by deficiency, 6 were eutrophic and 6 had malnutrition by excess (Figure 1). It is important to note that 13 cases required gastrostomy and the placement age was 40±47 months (range: 1 - 128 months).

Nutritional treatment: The average age for the beginning of treatment was 19±27 months, with an age range between 0.5 and 132 months. Of the total, 12 were under 6 years old, who received an average energy intake of: 83±43 kcal/kg/day, intact proteins: 0.5±0.2 gr/kg/day, PS proteins: 0.9±0.1 g/kg/day, Lys 68±18 mg/kg/day and L-carnitine 85±30 mg/kg/day. When comparing the intake with the international recommendations, it was observed that 3 cases complied with energy intake, 12 with protein intake from PS, 11 with total lysine intake and 8 cases for L-carnitine intake. The remaining 12 cases are older

Table 2. Post-Diagnostic Clinical Characteristics GA-1 (Group 1 and 2).

Case	Age at Start of Tx (month)	Sequelae	Abnormal Mov.	PDP	Pyramidal Syndrome	Epilepsy	Nutritional Status	Swallowing Disorder	PEG
1	6	Yes	Dystonia, oral-lingual dyskinesia	Severe DPD	No	No	O/W	Yes	Yes
2	15	Yes	Dystonia	Severe DPD	Yes	Yes	M	Yes	Yes
3	7	Yes	Dystonia, oral-lingual dyskinesia	Severe DPD	Yes	No	E	Yes	Yes
4	23	Yes	Dystonia, oral-lingual dyskinesia	Severe DPD	Yes	No	M	Yes	Yes
5	17	Yes	Dystonia, oral-lingual dyskinesia	Severe DPD	Yes	Yes	M	Yes	Yes
6	8	Yes	Dystonia, ballism	Severe DPD	Yes	No	E	Yes	Yes
7	132	Yes	Dystonia	Severe DPD	Yes	Yes	M	Yes	Yes
8	6	Yes	Dystonia	Severe DPD	Yes	No	M	Yes	Yes
9	9	Yes	Dystonia	Severe DPD	Yes	No	M	Yes	Yes
10	24	Yes	Dystonia	Severe DPD	Yes	Yes	M	Yes	Yes
11	49	Yes	Dystonia, ataxia	Moderate DPD	No	No	O/W	No	No
12	17	Yes	Dystonia	Mild DPD	No	No	RM	No	No
13	15	Yes	Dystonia	Moderate DPD	Yes	No	M	Yes	Yes
14	7	Yes	Dystonia	Mild DPD	Yes	No	RM	Yes	Yes
15	0.6	Yes	Dystonia	Severe DPD	No	No	E	No	No
16	8	Yes	Dystonia	Mild DPD	No	No	E	No	No
17	21	Yes	No	Moderate DPD	No	No	O/W	No	No
18	34	Yes	Dystonia	Mild DPD	No	No	RM	No	No
19	3	No	No	Normal	No	No	E	No	No
20	48	No	No	Normal	No	No	E	No	No
21	1	No	No	Normal	No	No	RM	No	Yes
22	8	No	No	Normal	No	No	O	No	No
23	0.5	No	No	Normal	No	No	O	No	No
24	7	No	No	Normal	No	No	O/W	No	No

T: Treatment, Mov: Movements, DPD: Delayed psychomotor development, D/O: Disorder, PEG: percutaneous endoscopic gastrostomy, RM: Risk of malnutrition, M: Malnourished, E: Eutrophic, O/W: Overweight, O: Obesity.

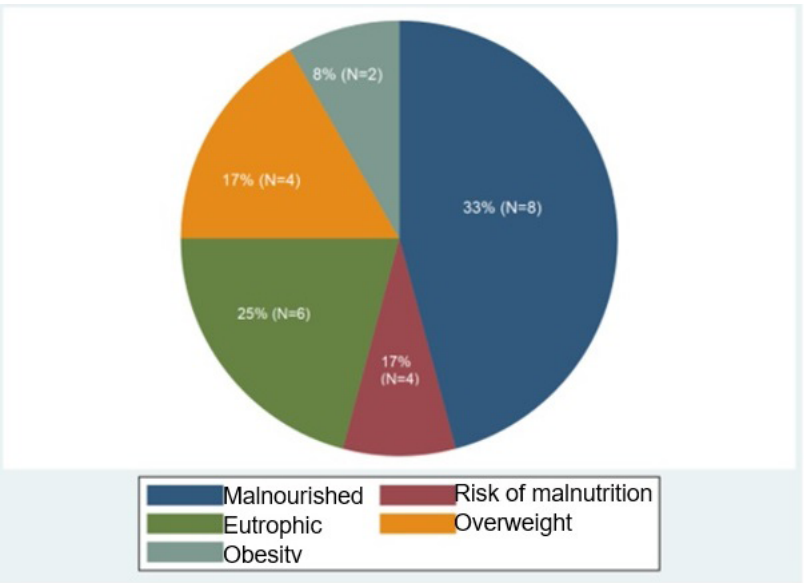

Figure 1. Evaluation of the nutritional status of the 24 subjects with AG-1.

than 6 years, who ingested an energy average of: 69±46 kcal/kg/day, intact protein: 0.9±0.2 gr/kg/day, PS protein: 0.9±0.7 gr/kg/day, Lys 71±26 mg/kg/day and L-carnitine 67±50 mg/kg/day. Of the total, 7 cases met energy recommendations, 9 cases met intact intake, only 3 cases received protein from PS and 8 cases for L-carnitine (Table 3). It should be noted that the group with AEC received an average energy intake of 95±54 kcal/day and the group without AEC of 62±31 kcal/day. This difference is due to the fact that 7/10 patients AEC are malnourished, therefore the caloric intake has increased to improve their nutritional status who could be affected by severe dystonia, as has been suggested in the literature [17].

The 24 GA-1 patients included in this study met the recommendations of iron, zinc and calcium, according to age, with the need to use pharmacological supplements in 50% of the cases.

Carnitine levels in plasma: 22 reported GA-1 patients (2 no data) had on average a total carnitine of 66±28 µmol/, a free carnitine of 50±20 µmol/L and an esterified carnitine of 17±14 µmol/L (Figure 2).

Table 3. Nutritional treatment in patients with GA-1 under the age of 6 years and over the age of 6 years.

Age	Energy (Kcal/kg/day)	Lysine (mg/kg/day)	PS (gr/kg/day)	Intact Protein (gr/kg/day)	Iron % adequacy	Calcium % adequacy	Zinc % adequacy
7-12 months (n:1)	95 (R:80)	92 (R:90)	0.9 (R:0.8-1)	____	66 (R:≥100)	162 (R:≥100)	217 (R:≥100)
1-3 years (n:7)	99±48 (R:81-94)	76±7 (R:60-80)	0.9±0.1 (R:0.8)	____	108±64 (R:≥100)	99±30 (R:≥100)	139±67 (R:≥100)
4-6 years (n:4)	52±15 (R:63-86)	47±12 (R:50-60)	0.9±0.2 (R:0.8)	____	126±33 (R:≥100)	81±23 (R:≥100)	100±36 (R:≥100)
6-10 years (n:7)	77±55 (R:66±5)	____	____	0.8±0.2 (R:0.9)	140±101 (R:≥100)	109±48 (R:≥100)	86±57 (R:≥100)
>11 years (n:5)	58±34 (R:54±3)	____	____	0.9±0.1 (R:0.9)	104±55 (R:≥100)	88±38 (R:≥100)	60±20 (R:≥100)

R: Reference (<6-year comparison with international protocol and >6-year comparison with recommendation for age)

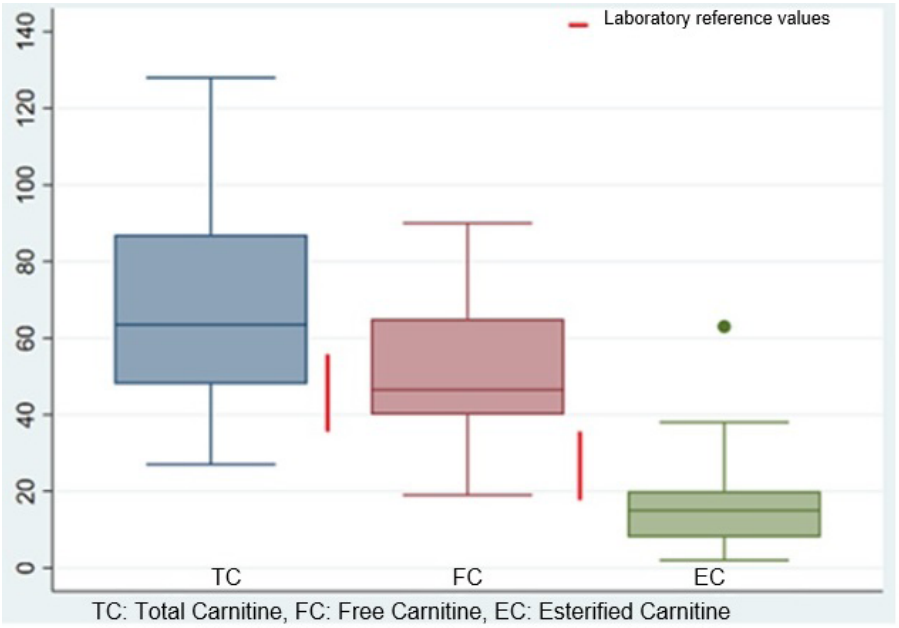

Figure 2. Plasma levels of total, free and esterified carnitine.
TC: Total Carnitine, FC: Free Carnitine, EC: Esterified Carnitine

Discussion

The age in which AEC clinically presented in this cohort was between 5 and 15 months, similar to that described in the literature, this could be correlated to an exponential increase in GA at the brain level in the critical period of development [9] . In relation to macrocephaly, the study detected that 88% of the subjects were born with it, which is over the 50% described in other studies [10] This could be explained by the fact that in these cases the clinical referral as a reason for neuropediatric consultation is made by a specialist in Chile, with macrocephaly being a frequent reason for consultation when inborn errors of metabolism are suspected [8].

In the study the patients who presented early AEC (10/24) evolved with neurological sequelae: abnormal movements type dystonic (located in hands and feet or generalized) accompanied by delay and/or regression of psychomotor development, hypotonic syndrome, pyramidal syndrome, which is consistent with what is described in the literature [6]. 58% of the cases (14/24) presented with an insidious start and neurological alterations without presenting AEC, this form of presentation is more prevalent in this population than in other cohorts studied according to what has been reported. However, it should be considered that the clinical manifestations of the neurological spectrum are what motivated the referral to specialists on inborn errors of metabolism, particularly in countries such as Chile, where GA-1 is not included in neonatal screening programs [4]

In the insidious forms they presented macrocephaly, accompanied by other neurological symptoms in a variable way such as psychomotor development delay and/or dystonia and hypotonia. This association of symptoms already previously described in the literature [14] should increase the index of diagnostic suspicion of GA-1, especially in countries that have not incorporated this condition into screening programs. Some studies relate the presence of alterations in the dorsolateral region of the putamen in patients with insidious start, and it has also been suggested that low adherence to nutritional treatment would be a high-risk factor for developing dystonia [11]. This point is difficult to objectively assess in the patients since the diagnosis was mostly made after the encephalopathic crisis or there are few imaging studies available. The neurological compromise of patients, oral dyskinesia and swallowing disorders increase energy demand and limit food intake, which compromises the patient's nutritional status. Therefore, it is important to raise the need for the application of a gastrostomy as early as possible in order to avoid catabolism [17]. Even in the insidious start forms, the need for gastrostomy placement was observed in 2 patients with malnutrition by deficiency.

According to the international follow-up protocol for GA-1 [8], in this group under 6 years old, 11/12 subjects met 2 important criteria such as the contribution of protein from PS and adequate intake of the amino acid Lys, which favors adequate growth and development. With respect to those over 6 years old, patients who still receive PS are in the process of abandonment and with an adequate intake of intact proteins according to the recommendation established for sex and age. It should be noted that energy intake is adjusted according to the nutritional status of the patient. Particularly in the group of patients older than 6 years, controversy has arisen regarding the need to maintain strict dietary therapy (Lys restriction) since the risk of AEC decreases considerably at this age. However, the current consensus [8], is to continue treatment beyond the age of 6 years, so maintaining monitoring with clinical and/or laboratory follow-up (free carnitine levels) could be considered in this group. This is given the clinical manifestations in GA-1 that are described even in adulthood, for example: white matter involvement and/or alteration of executive function [8].

The importance of maintaining a constant follow-up and education of the family to achieve good adherence to treatment and comply with medical indications, to prevent the risk of AEC and/or neurological impairment, must be stressed. This is consistent with the literature, since it is suggested that chronic follow-up be carried out in centers specializing in inborn errors of metabolism in order to achieve a better long-term prognosis [8]. Within the analysis of this study, it was verified that 3 cases of insidious start that had very low adherence to nutritional treatment and poor management of acute periods, currently present disabling generalized dystonia and one of them presented AEC after an infectious picture at age 12 months.

However, it must be emphasized that 5/6 patients with favorable evolution complied with the nutritional protocol for both PS or intact proteins and Lys intake, according to recommendations [8]. The favorable evolution in these cases is related to good adherence to treatment together with the early diagnosis and reinforces the concept that expanded neonatal screening programs does not necessarily guarantee normal neurological development.

It has been demonstrated that L-carnitine supplementation is important in the treatment of GA-1 since it contributes to preventing carnitine deficiency and in combination with actual nutritional management recommendations appears to improve neurological outcome [8,15]. It is suggested to start the supplementation with a dose of 100 mg/kg/day, but it is necessary to periodically measure the plasma value of free carnitine and to adjust the dose according to the reference range established by the laboratory. The study detected that 3 patients older than 6 years old who ingested less L-carnitine than the international recommendations (30 mg/kg/day of L-carnitine) maintained an average value of free carnitine over 40 µmol/L, considered adequate for the pathology. Together and according to what has been reported in other studies [5], all patients with GA-1 in the study had a free carnitine level within the normal range.

Conclusions

It is necessary to incorporate the GA-1 in the Chilean Neonatal Screening Program, as the symptoms and signs previous to the encephalopathic crisis are usually nonspecific and the

neurological consequences of a late diagnosis are invalidating as shown in this study. The clinical presentation of GA-1 is varied and the absence of AEC does not guarantee neurological indemnity. The presentation form of insidious start was prevalent in the analyzed population and the association of symptoms: Macrocephaly, developmental delay and/or regression, abnormal movements should increase diagnostic suspicion of AG-1.

To achieve a favorable nutritional and neurological evolution in the patient, active follow-up with continuous education of the family is of great importance in order to achieve adherence to nutritional treatment. Therefore, this should be done in specialized centers for inborn errors of metabolism to improve the prognosis of this condition.

Declaration of Conflicting Interests

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