

Correlation between neurological features, nutritional status and metabolic changes in patients with Ataxia-telangiectasia

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Abstract

Background

Ataxia-telangiectasia (AT) is an autosomal recessive neurodegenerative disorder caused by variants of *ATM* (ataxia telangiectasia mutated) gene. There is no specific treatment, but clinical management has advanced resulting in longer patient survival. However, these patients develop metabolic changes over time. We aimed to assess the correlation between neurological features, nutritional status and metabolic changes in AT patients.

Results

Significant correlations were found between the scores on the International Cooperative Ataxia Rating Scale (ICARS) and age ($r = 0.748$; $p < 0.001$), gamma glutamyl transferase (GGT) ($r = 0.743$; $p < 0.001$), insulin levels ($r = 0.520$; $p = 0.016$) and the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) index ($r = 0.585$; $p = 0.005$) as well as the scores on the Assessment and Rating of Ataxia (SARA) and age ($r = 0.704$; $p < 0.001$), GGT ($r = 0.701$; $p < 0.001$), insulin levels ($r = 0.706$; $p < 0.001$) and HOMA-IR index ($r = 0.764$; $p < 0.001$).

Conclusions

The relevant correlation between severity of ataxia and disease progression with metabolic changes such as liver function impairment and insulin resistance reinforce the importance to monitoring metabolic changes and evaluate nutritional status in these patients.

Background

Ataxia-telangiectasia (AT) is a rare autosomal recessive neurodegenerative disorder that usually starts in early childhood [1,2]. AT is caused by variants of *ATM* (ataxia telangiectasia mutated) gene encoded on chromosome 11q22-23, which causes failure of the ATM protein, a serine/threonine kinase that participates in cellular processes for maintaining genomic stability such as identification of errors, DNA repair and cell-cycle control [3].

AT is characterized by complex phenotypes comprising progressive cerebellar ataxia, ocular and cutaneous telangiectasia, oculomotor apraxia, immunodeficiency at varying degrees, increased predisposition for cancers, cellular radiosensitivity and malnutrition with loss of lean body mass [3–6]. The extended disease phenotype also includes growth retardation, premature aging, insulin resistance, hepatic impairment, type 2 diabetes, manifestations of mitochondrial dysfunction, inadequate responses to oxidative stress and increased cardiovascular risk [7].

Most typical symptoms of AT include early onset cerebellar ataxia and dilated capillaries at the angles of the eyes and on the skin (telangiectasia). In general, ataxia is the first major clinical sign, and usually starts around 5-year-old [8,9]. High serum levels of alpha-fetoprotein (AFP) is a relevant biomarker to confirm the diagnosis of AT [10].

To date, there is no specific treatment for AT. Advances in clinical management with multidisciplinary approaches have resulted in increased patient survival. However, these patients may develop metabolic changes and comorbidities that affect the disease course and their quality of life.

Studies conducted by our group have shown that age advanced is associated with insulin resistance and hepatic impairment in patients with AT [11,12]. With disease progression, AT patients usually present nutritional status impairment [13–18]. Thus, this study aimed to assess the correlation between neurological features, nutritional status and metabolic changes in patients with AT.

Methods

Patients

This is a cross-sectional study with prospective data from patients with AT (n = 25) who met the diagnostic clinical criteria of the European Society for Immunodeficiencies (ESID) [19]. The sample was comprised both male and female patients aged from 5 to 31 years who were followed up at the Division of Allergy, Clinical Immunology, Rheumatology and Neurology outpatient clinic of Universidade Federal de São Paulo (UNIFESP) Department of Pediatrics in São Paulo, Brazil.

The study was approved by UNIFESP Research Ethics Committee (nr. 0081/2018). All patients or their caregivers signed an informed consent to be enrolled in this study.

Anthropometric assessment

Anthropometric measurements included weight, height and skinfolds (tricipital, bicipital, subscapular and suprailiac) [20,21]. Those who were unable to stand were weighed on a digital wheelchair scale (Micheletti® electronic weighing platform for up to 500 kg). Recumbent height measurements were taken in supine position on a flat, firm surface by using a non-extensible tape (in millimeters).

For nutritional status classification, body mass index (BMI)-for-age z-scores and height-for-age z-scores for children and adolescents were calculated. Adults were classified according to BMI [20,22]. The sum of skinfold measures was used to estimate body composition [23–26].

The stage of pubertal development was self-assessed using the Tanner rating scale (Marshall & Tanner) [27].

Biochemical markers

Biochemical markers and metabolic tests evaluated included: alanine aminotransferase (ALT) (kinetic ultraviolet assay); aspartate aminotransferase (AST) (kinetic ultraviolet assay); gamma glutamyl transferase (GGT) (kinetic enzyme assay); fasting insulin and glucose (oxidase/peroxidase enzyme assay); and AFP (electrochemiluminescence assay). The Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) index was used to estimate peripheral insulin resistance.

Neurological assessment

Two rating scales, The International Cooperative Ataxia Rating Scale (ICARS) and the Scale for the Assessment and Rating of Ataxia (SARA), were applied by two skilled physical therapists to evaluate ataxia severity in all patients. General neurological examination and a routine brain magnetic resonance imaging (MRI) were also evaluated.

The ICARS is culturally adapted and validated for Brazil. This 19-item scale is divided into 4 subscales (scores 0-100): posture and gait disturbances (items 1 to 7; scores 0–34); limb ataxia (items 8 to 14; scores 0–52); dysarthria (items 15 and 16; scores 0–8); and oculomotor disorders (items 17 to 19; scores 0–6). ICARS cutoff points were: 1 to 30, mild ataxia; 31 to 60, moderate ataxia; and > 60, severe ataxia [28].

The second scale used was SARA, which has been translated into Brazilian Portuguese and validated for Brazil. It is an 8-item scale for a total score of 40: gait (0–8 points); stance (0–6 points); sitting (0–4 points); speech disturbance (0–6 points); finger chase (0–4 points); nose-finger test (0–4 points); fast alternating hand movements (0–4 points); and heel-shin slide (0–4) [29]. Ataxia was rated as mild (scores < 22, ability to walk with or without walking aids); moderate (scores 15–33, frequent use of wheelchair and ability to take a few steps with walking aid and use of upper limbs); or severe (scores > 30, bound to wheelchair) [30].

Statistical analysis

The data were entered into an Excel spreadsheet (Office Microsoft®) and analyzed using SPSS Statistics 19.0 (IBM®). Categorical variables were presented as absolute and percentage values. Continuous variables were analyzed for normality using the Shapiro-Wilk test. For comparisons between the two age groups evaluated, independent t-Student test was used to compare parametric variables (means and standard deviations) and the two-tailed Mann-Whitney U test was used to compare non-parametric variables (medians, minimum and maximum). Spearman's correlation coefficient was used to assess correlations. The level of statistical significance was set at 5% ($p < 0.05$).

Results

From the sample of 25 patients with AT evaluated, 16/25 (64%) were male, the median age of 13 (5–31) years. The median age at diagnosis was 4.0 (1–16) years. Family history of consanguinity was documented in 13/25 (52%) patients. Cerebellar atrophy was detected in 15/18 (83.3%) patients who underwent brain MRI.

Regarding nutritional status, 8/25 (32%) were malnourished; only 1/25 (4%) was overweight; and 8/19 (42%) showed short stature for age. The assessment of the body fat composition revealed low percentage of body fat in 4/24 (16.6%) and high percentage of body fat in 7/24 (29.1%). Low lean body mass was seen in 13/24 (54.1%) patients.

As for neurological manifestations, mean age of symptom onset was 10 (\pm 4.3) months. Cerebellar ataxia was the most common sign seen in 15/25 (60%) patients. Mean age of loss of independent gait was 8 (\pm 2.0) years; 13/25 (52%) patients had the ability of walking with aid and 5/25 (20%) showed inability to walk.

ICARS scores indicated moderate ataxia in 13/25 (52%) patients and severe in 9/25 (36%). SARA scores indicated moderate ataxia in 9/25 (36%) patients and severe in 9/25 (36%). Table 1 shows the characteristics of patients with A-T.

Table 1 Characteristics of patients with AT

Our sample was classified into two age groups (\leq 12 years; $>$ 12 years) to compare biochemical markers. Significant differences were found between the age groups for ALT ($p = 0.017$), GGT ($p < 0.001$) and AFP ($p = 0.006$). Table 2 shows the comparison of biochemical markers between the two age groups. Figure 1 shows the comparison of GGT, ALT and AFP results between these groups.

Table 2 Comparison of biochemical markers in patients with AT by age groups

Figure 1 Boxplot of GGT (a); boxplot of ALT (b); and boxplot of AFP (c) for the age groups \leq 12 years ($n = 10$) and $>$ 12 years ($n = 15$)

The median score on ICARS was 57 (7–87). Significant direct correlations were found between ICARS scores and age ($r = 0.748$; $p < 0.001$), GGT ($r = 0.743$; $p < 0.001$), insulin ($r = 0.520$; $p = 0.016$), and HOMA-IR index ($r = 0.585$; $p = 0.005$). There was a trend towards indirect significance of the correlation between these scores and height-for-age z-scores ($r = -0.427$; $p = 0.068$).

The median score on SARA was 20.5 (3–32). Significant direct correlations were seen between SARA scores and age ($\rho = 0.704$; $p < 0.001$), GGT ($r = 0.701$; $p < 0.001$), insulin ($r = 0.706$; $p < 0.001$), and HOMA-IR index ($r = 0.764$; $p < 0.001$). There was an indirect correlation of these scores with height-for-age z-scores ($r = -0.462$; $p = 0.046$).

A strong correlation was found between the two rating scales ($r = 0.900$; $p < 0.001$). Figure 2 shows the correlation between ICARS and SARA scores and age.

Figure 2 (a) Scatterplot of SARA and ICARS scores; (b) Scatterplot of ICARS scores versus age; and (c) Scatterplot of SARA scores versus age (c)

Discussion

Our study found a marked correlation between severity of ataxia and nutritional and metabolic changes in patients with AT. Statistical analysis showed significant difference when ICARS and SARA rating scales were compared with, GGT, fasting insulin and HOMA-IR index. It is noteworthy that both ICARS and SARA were able to detect those patients with severe ataxia, which evidences their rating agreement especially for the most severe form of the disease. This study shows correlations between worsening of ataxia manifestations with age and metabolic changes including impairment of liver function and insulin resistance in patients with AT.

Patients with AT may develop diabetes as a complication in late adolescence and they usually present with high blood glucose levels without glycosuria or ketosis and high levels of insulin in response to glucose administration [31]. Two studies with patients with AT undergoing the 2-hour oral glucose tolerance test reported increased postprandial blood glucose levels and insulin resistance [11,32].

Some previous data have shown that insulin acts on all types of cells in the central nervous system (CNS) including neurons, astrocytes, oligodendrocytes, ependymal cells, brain endothelial cells and microglia. In fact, all cell types in the CNS express insulin receptors, which suggests their ability to respond to insulin. On a functional basis, insulin resistance can affect brain function and result in cognitive and neurodegenerative changes which could explain our findings [33].

Chronic liver dysfunction can lead to the accumulation of toxic metabolites in the brain and cause neuroinflammation by increasing pro-inflammatory cytokines and oxidative and nitrosative stress (nitric oxide) [34]. A recent retrospective cohort study of 67 patients with AT aged 1 to 38 years found a significant correlation between Klockgether ataxia score (KAS) and GGT and age, which corroborates our findings [35]. Our results suggest that liver dysfunction in patients with AT may indicate greater disease severity and more severe neurological symptoms. Therefore, it is recommended to evaluate liver function (especially GGT) as part of routine evaluations in patients with AT as GGT seems to have a more significant relationship with neurological decline.

A comparison of biochemical markers between the age groups (≤ 12 years and > 12 years) in our study revealed that liver enzyme, ALT, GGT and AFP, were significantly higher among older patients. Elevated AFP levels are characteristic of AT and they apparently increase with age [10].

Regarding liver enzymes, a study carried out by our group found that levels of ALT and AST were more significantly altered from adolescence in patients with AT. Those patients who developed liver dysfunction tended to be older and had higher sum of insulin levels than those with hepatic steatosis only or no liver dysfunction [11]. Donath et al. reported steady elevation of ALT and GGT levels from the age of 12 in AT, which is in line with our results [35]. Weiss et al. reported elevated liver enzymes in young AT patients (age 9.97 ± 5.09 years) associated with dyslipidemia, but not with age [36].

Most patients with AT, particularly those with the classic form of the disease, have malnutrition and stunted growth even with adequate energy intake. It is thus believed to be a multifactorial condition associated with the severity of neurological impairment [8]. Although we did not find a significant

correlation between ataxia scores and BMI, all eight patients with malnutrition, regardless of their age, showed moderate or severe ataxia. Moreover, stunted growth may also be associated with neurological decline in these patients as there was a significant indirect correlation of SARA scores and a trend towards significance of ICARS scores with height-for-age z-scores.

This study has some limitations. First, *ATM* gene variants were not genotyped in the patients with AT evaluated. Second, hepatic biopsies and additional nutritional assessments were not performed. Third, serial brain imaging studies were not conducted.

In conclusion, our study demonstrates a relevant correlation between severity of ataxia and disease progression with metabolic changes such as liver function impairment and insulin resistance in patients with AT. Therefore, with disease progression patients with AT may present with liver dysfunction and insulin resistance, and these findings reinforce the importance to monitoring metabolic changes and evaluate nutritional status in these patients.

Table 1
Characteristics of patients with AT

Variables		N (%)
Age (years) (n = 25)	5–12	10 (40.0%)
	13–31	15 (60.0%)
Nutritional status (n = 25)	Underweight	8 (32.0%)
	Normal weight	16 (64.0%)
	Overweight	1 (4.0%)
Body fat mass (n = 24)	Low	4 (16.6%)
	Normal	13 (54.1%)
	High	7 (29.1%)
MUAC (n = 24)	Low	13 (54.1%)
	Normal	8 (44.4%)
Sexual maturation staging (n = 25)	Prepubertal	7 (28.0%)
	Pubertal	11 (44.0%)
	Late pubertal	7 (28.0%)
Symptom at disease onset (n = 25)	Ataxic gait	15 (60.0%)
	Hypotonus	7 (28.0%)
	Ocular telangiectasia	3 (12.0%)
Gait (n = 25)	Walking without aid	7 (28.0%)
	Walking with aid	13 (52.0%)
	Inability to walk	5 (20.0%)
ICARS scores (n = 25)	Mild ataxia	3 (12,0%)
	Moderate ataxia	13 (52%)
	Severe ataxia	9 (36%)
SARA scores (n = 25)	Mild ataxia	7 (28.0%)
	Moderate ataxia	9 (36.0%)
	Severe ataxia	9 (36.0%)
Abbreviations: MUAC: mid-upper arm circumference; ICARS; The International Cooperative Ataxia Rating Scale; SARA: Scale for the Assessment and Rating of Ataxia; N (%): absolute value and percent.		

Table 2
Comparison of biochemical markers in patients with AT by age groups

Variables		Age group 1 (≤ 12 years) (n = 10)	Age group 2 (> 12 years) (n = 15)	p-value ^{a,b}
AST	U/L	29.9 (16.6–74.3) ^c	37.7 (16.6–82.3)	0.360 ^a
ALT	U/L	18.4 (11.4–45.0)	31.4 (16.3–144.5)	0.017^a
GGT	U/L	17.5 (7.0–97.0)	37.0 (21.0–612.0)	< 0.001^a
Fasting glucose	mg/dL	87.1 (± 8.4) ^d	87.4 (± 12.1)	0.950 ^b
Fasting insulin	μIU/mL	5.9 (0.4–22.0)	7.3 (3.3–80.1)	0.102 ^a
AFP	IU/mL	165.1 (± 89.4)	345.8 (± 171.4)	0.006^b
HOMA-IR index		1.15 (0.07–4.44)	1.75 (0.51–20.94)	0.102 ^a
Abbreviations: AST: aspartate aminotransferase; ALT: alanine aminotransferase; AFP: alpha-fetoprotein; HOMA-IR: Homeostasis Model Assessment for Insulin Resistance.				
^a Level of significance for Mann-Whitney U-test				
^b Level of significance for independent Student's t-test				
^c Median (minimum-maximum)				
^d Mean (standard deviation)				

Abbreviations

AFP - Alpha-fetoprotein

ALT – Alanine aminotransferase

AST – Aspartate aminotransferase

AT – Ataxia-telangiectasia

ATM – Ataxia telangiectasia mutated

BMI – Body mass index

CNS - Central nervous system

GGT - Gamma glutamyl transferase

ESID - European Society for Immunodeficiencies

HOMA-IR - Homeostasis Model Assessment for Insulin Resistance

ICARS - International Cooperative Ataxia Rating Scale

KAS - Klockgether ataxia score

SARA - Assessment and Rating of Ataxia

ZE/I - Height-for-age z-scores

ZIMC/I - Body mass index-for-age z-scores

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee in Research of the Universidade Federal de São Paulo (UNIFESP), identification number 0081/2018.

Consent for publication

Patients and parents gave consent to be included in the study through consent form.

Availability of data and material

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

Funding

Nothing to disclose.

Authors' contributions

TLNB: Acquisition of data; drafting of the manuscript; statistical analysis and interpretation of data of the manuscript.

IRR: Acquisition of data and critical revision for important intellectual content.

KKT: Acquisition of neurological data.

FAM: Acquisition of neurological data.

JLP: Study supervision and critical revision for important intellectual content.

OGPB: Study supervision and critical revision for important intellectual content.

FLAF: Carried out the biochemical analysis.

ACF: Carried out the biochemical analysis.

CSA: Study supervision and critical revision for important intellectual content.

ROSS: Concept and design development; drafting of the manuscript; study supervision and critical revision for important intellectual content.

All authors read and approved the final manuscript.

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Figures

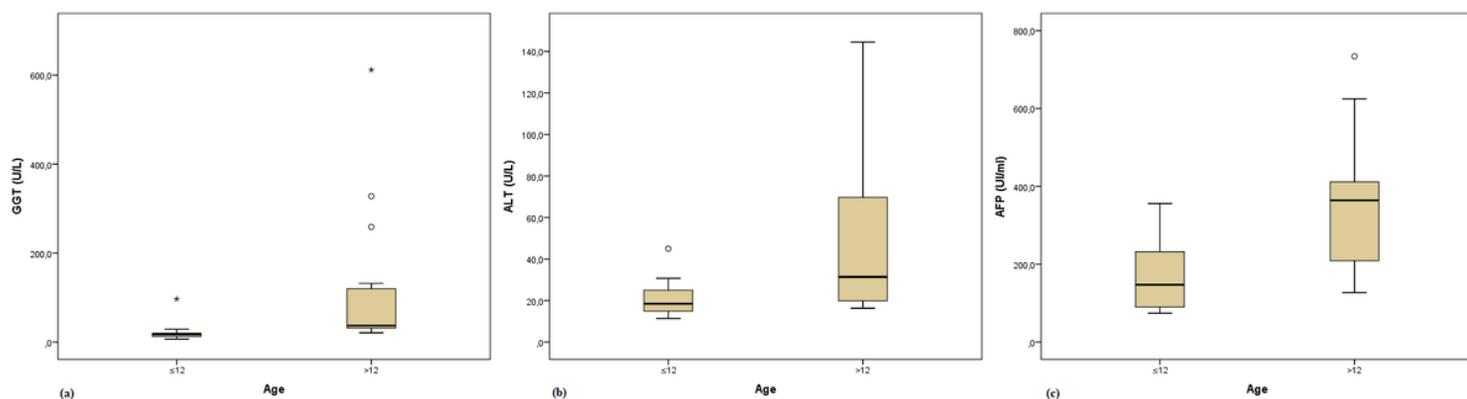


Figure 1

Boxplot of GGT (a); boxplot of ALT (b); and boxplot of AFP (c) for the age groups ≤ 12 years ($n = 10$) and >12 years ($n = 15$)

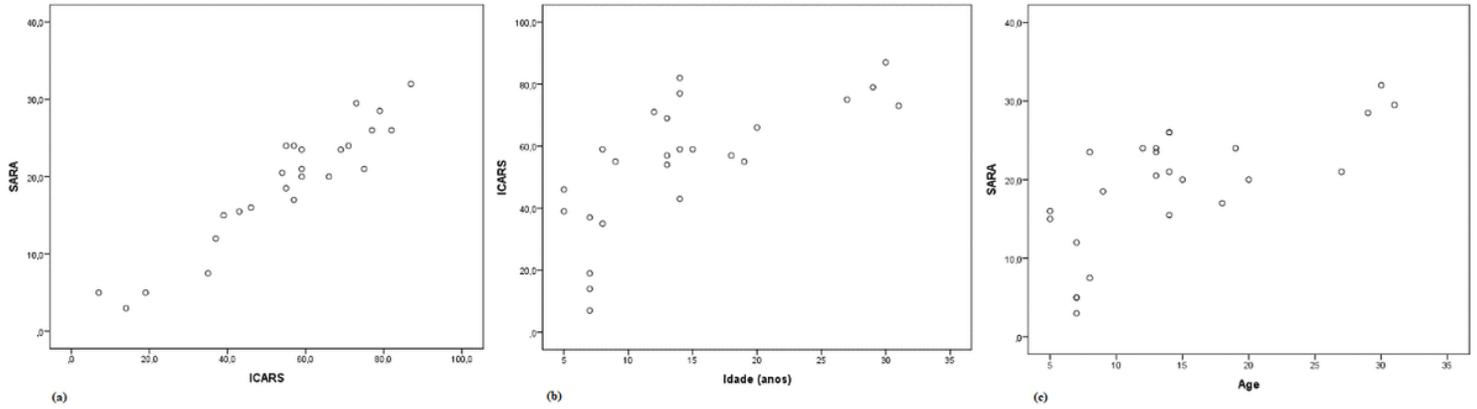


Figure 2

(a) Scatterplot of SARA and ICARS scores; (b) Scatterplot of ICARS scores versus age; and (c) Scatterplot of SARA scores versus age (c)