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Evaluation of Clinical and Magnetic Resonance Spectroscopy Characterization of Patients with Ataxia Telengectisa

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ABSTRACT

Background: Ataxia can be a symptom of a wide range of neurological illnesses. Neurochemical alterations can be detected non-invasively using magnetic resonance spectroscopy (MRS).

Objective: This study aimed to reach to an early diagnosis of the neurometabolic changes of Ataxia Telangiectasia via describing the causes & clinical features of this disease and determining the functional changes in brain tissue in patients with it.

Patients and Methods: All children with Ataxia Telangiectasia (eighteen) attending to Pediatric Department, Zagazig University Hospitals. The patients were subjected to complete history taking, full clinical examination, application of Scale for the assessment and rating of ataxia (SARA) and MRS imaging.

Results: Study participants were found to have a statistically significant correlation between their overall SARA score and their gender. Total score was significantly higher in female patients. In addition, correlations between total SARA score and skin nodules, hepatosplenomegaly were statistically significant. Patients with skin nodules and hepatosplenomegaly (HSM) have significantly lower total score. MRI results and HSM results had a statistically significant relationship.

Conclusion: MRS and SARA are useful tools in studying the causes, clinical picture, diagnosis & treatment of Ataxia Telangiectasia.

Keywords: Ataxia Telangiectasia, Magnetic resonance spectroscopy.

INTRODUCTION

There are numerous conditions that can cause ataxia, which is characterized by a lack of coordination and balance in movement and posture. The intricate circuitry linking the basal ganglia, cerebellum, and cerebral cortex is mostly to blame [(1)]. Ataxia Telangiectasia (AT) is an autosomal recessive multisystem genetic neurodegenerative and immune deficiency disorder, telangiectasia, is a global rare condition. It has a bad prognosis because of its usual shape. Ataxia, ocular apraxia and peripheral neuropathy are just some of the neurological symptoms that can occur as a result of axonal neuropathy. Movement disorders such as dystonia, choreoathetosis and myoclonus are also common. Parkinsonism, telangiectasias, elevated alpha-fetoprotein and reduced IgA levels, and radio hypersensitivity are also possible symptoms [(2)]. Ataxia mutations in the ATM gene, which is essential for controlling the cell cycle and responding to DNA double strand break damage and chromatin alterations, cause telangiectasia. Only symptomatic treatments have been available up until now, and their efficacy is dependent on the severity of the phenotypic [(3)].

Ataxia in children might be difficult to detect. A delay in coordination may be mistaken for this condition in very young children. Its clinical signs can be spotted with a thorough physical examination and precise maneuvers. Ataxia is caused by a variety of factors, all of which can have varying degrees of severity ranging from mild and transitory to extremely severe and frightening. A pediatrician must be adept at distinguishing between curable conditions and those that are degenerative and fatal, some of which are extremely difficult to identify [(4)].

Schmitz-Hübsch *et al.* [(5)] developed the Scale for the Assessment and Rating of Ataxia (SARA) as a clinical tool for assessing various ataxia-related disabilities. Gait and stance, sitting, disturbance of speech, finger-chase test, nose-finger test, quick alternating movements and heel-shin test" are all included on a scale that indicates eight categories. " [(6)]. The International Cooperative Ataxia Rating Scale (ICARS) was replaced by SARA because of the ICARS's excessive number of evaluation points. SARA is a popular replacement for the previous scale because it has a smaller number of elements [(7)].

Neurometabolite levels such as amino acids, lipids, lactate, alanine, N-acetyl aspartate, choline, creatine, and myoinositol can be measured using magnetic resonance spectroscopy (MRS), which is a non-invasive diagnostic technique [(8)]. Anatomical tissue changes can be detected using Magnetic Resonance Imaging (MRI), whereas functional tissue changes can be detected using MRS investigations by measuring changes in cell metabolite concentrations. When comparing Ataxia Telangiectasia research, there are inconsistent outcomes [(9)].

It was the goal of this work to reach an early diagnosis of the neurometabolic changes of Ataxia Telangiectasia via describing the causes & clinical features of this disease and determining the functional changes in brain tissue in patients with it.

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SUBJECTS AND METHODS

Eighteen patients at Zagazig University Hospitals, at Primary Immune-deficiency Unit, Pediatric Department served as the subjects for this cross-sectional trial.

Inclusion criteria: Children diagnosed with ataxia telangiectasia and both sexes.
Exclusion criteria: Patients with ataxia due to any other causes rather than ataxia telangiectasia.

The participants were subjected to the following:
History: The patient's age, sex, gender, maternal risk factors, gestational age, prenatal, natal history were all recorded in a thorough medical history.

Clinical examination:

General, and neurological examinations were done to all patients. Eight items of SARA scale were tested including 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 movement (0-4 points) and heel-shin slide (0-4 points). The severity of ataxia is determined by calculating the sum of the eight categories. Assessments of the four limbs (items 5-8) were done bilaterally, and the mean values were utilised to calculate the total score for these activities [(5)].

MR imaging techniques:

All MR sequences were done using 1.5 Tesla superconducting MR imager (Achieva-class IIa, Philips medical system). Supine examinations were carried out utilizing a conventional brain-coiling device. T1-weighted images of the patient's sagittal, coronal, and axial planes were taken to verify the patient's precise location and to serve as a reference point for subsequent sections. MRI images showed some patient with cerebellar atrophy characterized by prominent cerebellar folia which appear widened with capacious fourth ventricle & retro-cerebellar CSF space **(Figure 1).**

MRI images also detected some accidental non-symptomatic findings like cerebellar granulomas. **(Figure 2)**.

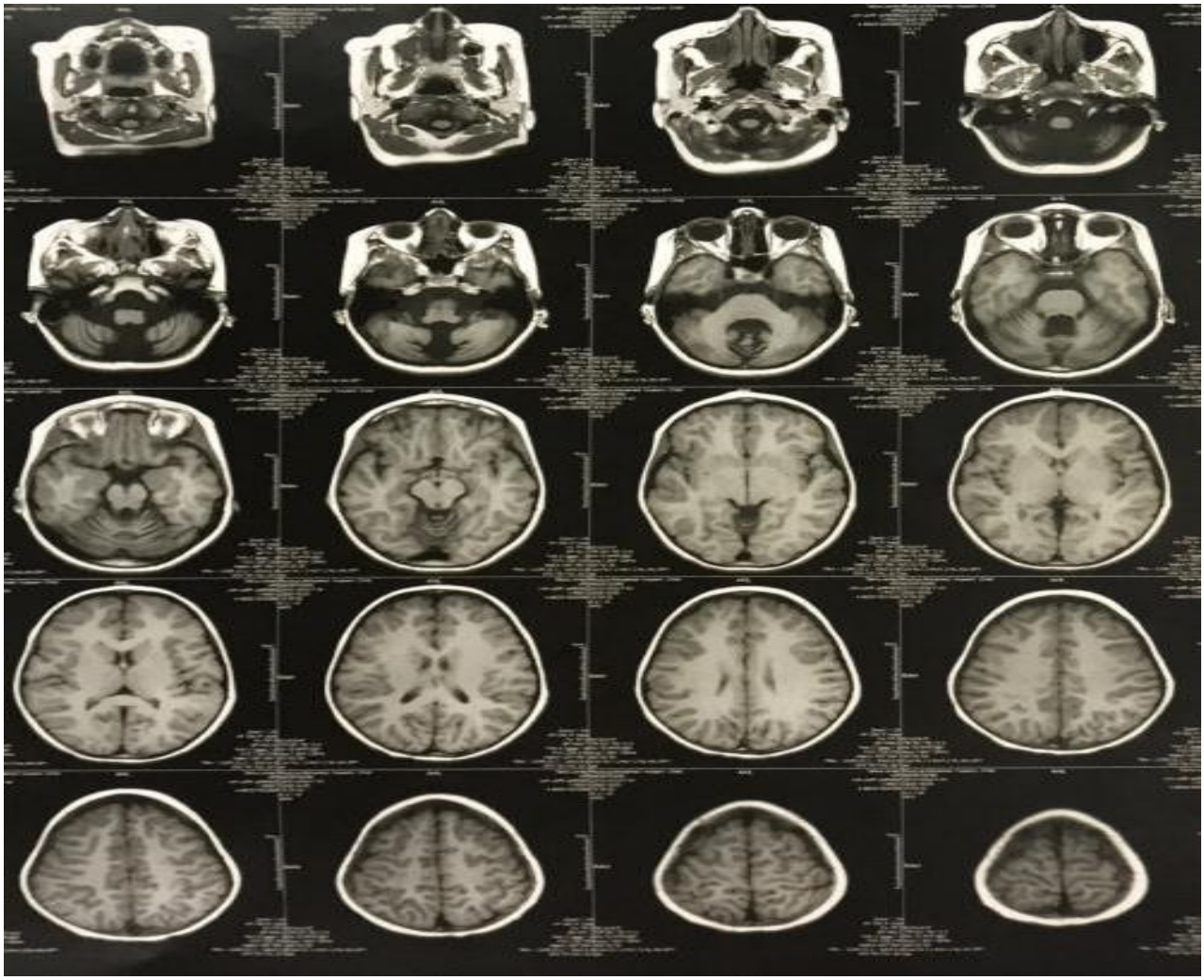

Figure (1): Showing MRI of cerebellar atrophy

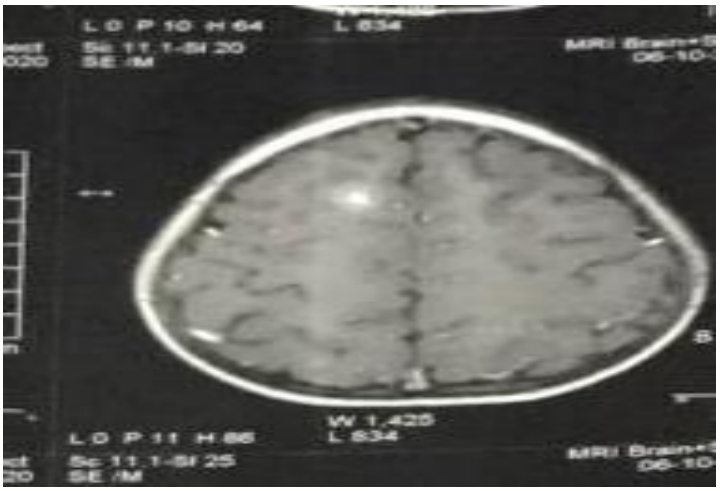

Figure (2): Showing MRI of cerebral granuloma

Proton MR spectroscopy (H^1 MRS):

Technique and pulse sequences:

*PRESS (Point Resolved Spectroscopy).

*Water suppression of dominant water signal by CHESS technique.

*Fat suppression saturation bands next to VOI as well as magnetic shimming were performed automatically at the beginning of SVS.

***Qualitative** assessment of the MRS curve: Frequency domain curve was fitted by the manufacturer to define N-acetyle aspartate (NAA), choline containing components (Cho), myo-inositol (mI), creatine and phosphocreatine (Cr) peaks as follow: NAA at 2.02 ppm, Cho at 3.22ppm, Cr at 3.01ppm and myoinisitol at 3.56ppm.

***Quantitative** assessment of the MRS metabolites: Absolute values of NAA, Cho, Cr & mI comparing it with control group as well as calculation of metabolic ratios of NAA/Cho, NAA/Cr, Cho/Cr and mI/Cr comparing it with control group.

MRS results of cerebral granuloma showed increased choline with mild reduction of creatine and NAA, while increased CHO/CR & CHO/NAA ratios **(Figure 3).**

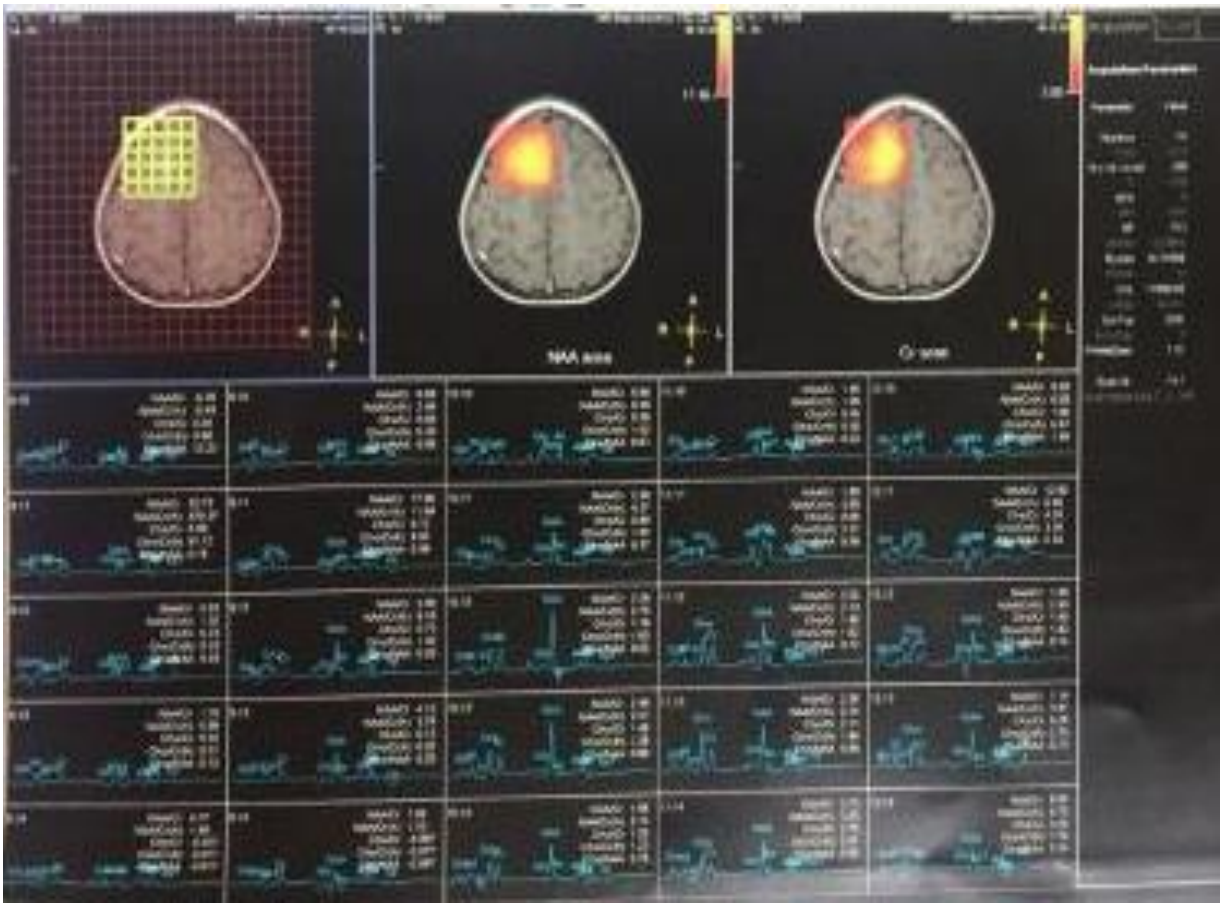

Figure (3): Showing abnormal MRS of cerebral granuloma

Ethical approval:

Zagazig University's research ethics committee approved the study. Every participants' parent signed informed consent forms and submitted them to Zagazig University (ZU-IRB#6862). We adhered to the Helsinki Declaration, the ethical guideline of the World Health Organization for human trials.

Statistical analysis

The independent t-test (t) and the Mann-Whitney (MW) tests were employed to compare parametric and non-parametric data respectively on SPSS version 23, in the analysis of the differences between the groups. When there was a difference between two groups of non-parametric data, proportions were compared using the Chi-square test (X^2). Diagnostic and prognostic utility in newborn sepsis were evaluated using Receiver Operating Characteristics (ROC) analysis. Cut-off points and their associated values. P value ≤ 0.05 was considered statistically significant (S). It was judged highly significant (HS) when the P value was 0.001 and non-significant (NS) when the P value was > 0.05.

RESULTS

Male represented 38.88% of the studied patients. Age of patients ranged from 4 to 10 years with a mean age of 7.17 years (Table 1).

Table (1): Qualitative demographic data

	N=18 (%)
Gender: Male Female	 7 (38.88%) 11 (61.11%)
Age (years) Mean ± SD Range	 7.17 ± 2.48 4 – 10

The total SARA score and the gender of patients have a statistically significant relationship. In female patients, the total score was much greater (Table 2).

Table (2): Relation between SARA score and demographic data of the studied patients

Parameters	**SARA score**		**Test**	
	Mean ± SD	**Range**	**t**	**P**
Gender: Male Female	 15.86 ± 6.41 21.91 ± 4.3	 10 – 24 15 – 27	-2.57	0.03*

Nodules on the skin had a statistically significant correlation with the total SARA score. Patients with skin nodule had significantly lower total score. Hepatosplenomegaly had a statistically significant correlation with the total SARA score. Patients with HSM had significantly lower total score (Table 3).

Table (3): Relation between SARA score and clinical data of the studied patients

Parameters	**SARA score**		**Test**	
	Mean ± SD	**Range**	**t**	**P**
Ataxia: Present	 20.17 ± 6.16	 10 – 27	-	-
Nystagmus: Present	 20.17 ± 6.16	 10 – 27	-	-
Telangiectasia: Present	 20.17 ± 6.16	 10 – 27	-	-
Tremor: Present	 20.17 ± 6.16	 10 – 27	-	-
Skin nodule: Absent Present	 22.86 ± 3.8 10.75 ± 0.5	 15 – 27 10 – 11	6.22	<0.001**
Immune deficiency: Present	 20.17±6.16	 10-27	-	-
Hepato-splenomegaly: Absent Present	 20.87 ± 6.52 16.67 ± 1.53	 10 – 27 15 – 18	2.21	0.043*

There was statistically significant positive correlation between total SARA score and each of patients' age, weight, height and head circumference. On the other hand, there was statistically non-significant negative correlation between total SARA score and BMI (Table 4).

Table (4): Correlation between SARA score and both age and anthropometric measures

	SARA score	
	R	P
Age (year)	0.91	<0.001**
Weight (kg)	0.73	<0.001**
Height (cm)	0.97	<0.001**
BMI (kg/m^2)	-0.31	0.219
Head circumference (cm)	0.78	<0.001**

The total SARA score and MRI findings in the research subjects had a statistically non-significant relationship. Patients with findings suggestive of cerebellar atrophy had higher total score. There was statistically significant relation between total SARA score and MRS findings. Patients with normal MRS have significantly lower total score (Table 5).

Table (5): Relation between SARA score and radiological investigation of the studied patients

Parameters	SARA score		Test	
	Mean ± SD	Range	F	P
MRI:				
Normal	18.33 ± 7.42	10 – 27		
Cerebellar atrophy	24.67 ± 1.51	23 – 27	3.1	0.075
Cerebral granuloma	16.67 ± 1.53	15 – 18		
MRS:				
Normal	20.87 ± 6.52	10 – 27	2.209	0.043*
High CHO/CR &CHO/NAA ratio	16.67 ± 1.53	15 – 18		

The best cut off of total SARA score in diagnosis of abnormal MRI findings was ≥ 22.5 with area under curve, sensitivity of 66.7%, specificity of 66.7%, positive predictive value (PPV) of 66.7%, negative predictive value (NPV) of 66.7% and accuracy of 66.7% (p > 0.05) (Table 6, Figure 4).

Table (6): Performance of total SARA score in prediction of abnormal MRI findings among the studied patients

Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	P
≥22.5	0.648	66.7%	66.7%	667%	66.7%	66.7%	0.289

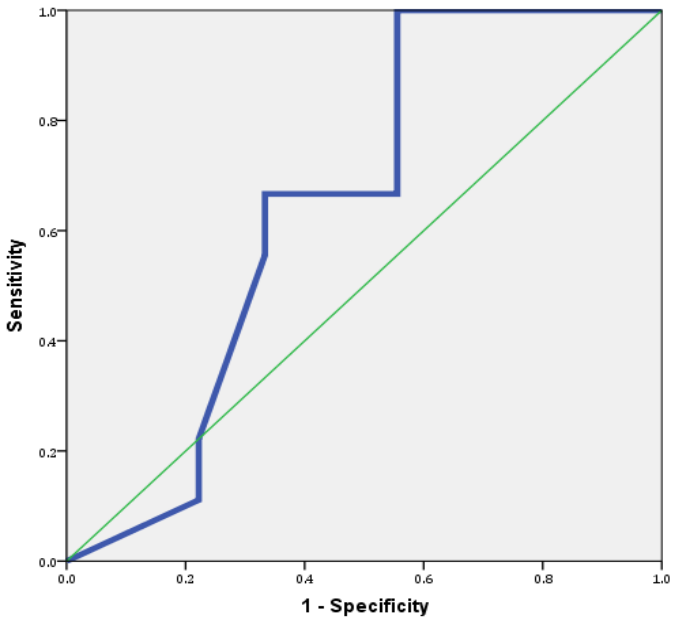

Figure (4): ROC curve showing performance of total SARA score in prediction of abnormal MRI findings among the studied patients.

MRI findings and the existence of HSM had a statistically significant relationship. All patients with HSM had cerebral granuloma on MRI evaluation. Skin nodules and the total SARA score had a statistically insignificant relationship **(Table 7).**

Table (7): Relation between MRI findings and clinical data of the studied patients

Parameters	MRI			
	Normal N=9 (%)	**Cerebellar atrophy N=6 (%)**	**Cerebral granuloma N=3 (%)**	**P**
Ataxia: Present	9 (100%)	6 (100%)	3 (100%)	-
Nystagmus: Present	9 (100%)	6 (100%)	3 (100%)	-
Telangiectasia: Present	9 (100%)	6 (100%)	3 (100%)	-
Tremor: Present	9 (100%)	6 (100%)	3 (100%)	-
Immune deficiency: Present	9 (100%)	6 (100%)	3 (100%)	-
Skin nodule: Absent Present	5 (55.6%) 4 (44.4%)	6 (100%) 0 (0%)	3 (100%) 0 (0)	0.126
Hepato-splenomegaly: Absent Present	9 (100%) 0 (0%)	6 (100%) 0 (0%)	0 (0%) 3 (100%)	<0.001**

There was statistically significant relation between MRS findings and presence of HSM. All MRS results were abnormal in patients with HSM. There was no correlation between the MRS results and anything else including presence of skin nodules **(Table 8)**

Table (8): Relation between MRS findings and clinical data of the studied patients

Parameters	MRS		Test	
	Normal N=15 (%)	**Abnormal N=3 (%)**	**χ^2**	**P**
Ataxia: Present	15 (100%)	3 (100%)	-	-
Nystagmus: Present	15 (100%)	3 (100%)	-	-
Telangiectasia: Present	15 (100%)	3 (100%)	-	-
Tremor: Present	15 (100%)	3 (100%)	-	-
Immune deficiency: Present	15(100%)	3(100%)	-	-
Skin nodule: Absent Present	11 (73.3%) 4 (26.7%)	3 (100%) 0 (0%)	Fisher	> 0.999
Hepato-splenomegaly: Absent Present	15 (100%) 0 (0%)	0 (0%) 3 (100%)	Fisher	0.001**

DISCUSSION

Ataxia Telangiectasia, an autosomal recessive cerebellar ataxia, affects one in 50,000 people. There are several other names for this illness, including genomic instability, chromosomal instability, DNA damage response, and even neurocutaneous syndrome [(10)]. **Duarte *et al.*** [(11)] proved the non-invasive detection of millimolar concentrations of endogenous metabolites in chosen tissue volumes that give biochemical information unavailable from traditional structural MRI, which is used to detect anatomical tissue morphological changes in specified tissue volumes.

In our study, regarding the demographic data of the studied patients, male represented 38.88%. Age of patients ranged from 4 to 10 years with a mean age of 7.17 years. Anthropometric measurements showed that the weight of the studied patients ranged from 15 to 36 kg with a mean of 20.83 kg. The height ranged from 90 to 125 cm with a mean of 109.56 cm. BMI of patients ranged from 14.83 to 23.07 kg/m^2 with a mean of 17.22 kg/m^2. Head circumference ranged from 48 to 53 cm with a mean of 49.72 cm. In a similar study conducted by **Ehlayel *et al.*** [(12)], it was determined that 18 youngsters with Asperger's syndrome have been studied. The average age of the participants in the study was 76.9 months, split evenly between men and women. Seventy-seven percent had a history of AT in their family, while 41.7% of the participants had parents who were related by blood.

During our study, we assessed the distribution of the studied patients regarding SARA score domains. Gait domain scores ranged from 1 to 5 with a mean of 2.61. Stance domain scores ranged from 1 to 5 with a mean of 3.22. Sitting domain scores ranged from 1 to 2 with a mean of 1.5. Speech disturbance domain scores ranged from 2 to 4 with a mean of 2.94. Finger chase domain scores ranged from 1 to 4 with a mean of 2.17. Nose finger test domain scores ranged from 1 to 4 with a mean of 3.17. Fast alternating domain scores ranged from 1 to 4 with a mean of 2.39. Heel shin side domain scores ranged from 2 to 3 with a mean of 2.28. SARA total score of the patients ranged from 10 to 27 with a mean of 20.17.

Our results cleared that there was a statistically significant relation between total SARA score and gender of patients. Total score was significantly higher in female patients. In addition, there was statistically significant relation between total SARA score and presence of skin nodules and presence of hepatosplenomegaly (HSM). Patients with skin nodules and presence of hepatosplenomegaly (HSM) had significantly lower total score. The results of **Schmitz *et al.*** [(5)] are consistent with our results. Both showed that SARA score increased with progressing disease ($P < 0.001$).

Regarding the correlation between SARA score and both age and anthropometric measures, there was statistically significant positive correlation between total SARA score and each of patients' age, weight, height, and head circumference. On the other hand, there was statistically non-significant negative correlation between total SARA score and BMI. On the contrast to our results, **Lawerman *et al.*** [(13)] conducted a study in which cross-sectional SARA ratings and age or disease duration were found to be unrelated, according to the research.

Our study also showed that there was statistically non-significant relation between total SARA score and MRI findings of the studied patients. Patients with findings suggestive of cerebellar atrophy had higher total score. There was statistically significant relation between total SARA score and MRS findings. Patients with normal MRS had significantly lower total score.

We also evaluated the performance of total SARA score in prediction of abnormal MRI findings among the patients in our study using the ROC curve. We found that the best cut off value of total SARA score in diagnosis of abnormal MRI findings was ≥22.5 with area under curve, sensitivity of 66.7%, specificity of 66.7%, positive predictive value (PPV) of 66.7%, negative predictive value (NPV) of 66.7% and accuracy of 66.7% ($p > 0.05$). **Ehlayel *et al.*** [(12)] studied the correlation of AT clinical findings and MRI grade of cerebellar atrophy. Ten patients had data on both AT clinical findings and MRI cerebellar atrophy grades and revealed correlation (coefficient $r = 0.566$), but it was not statistically significant ($p = 0.088$, 95% CI for $r = -0.2790$ to 0.8321). **Farr *et al.*** [(14)] described the existence of cerebellar atrophy, which is typical of classical AT, despite the relative preservation of neurologic function. They showed that cerebellar cortical volume alone plays a very limited role in the immediate expression of the neurodegeneration of AT. Degeneration of the extrapyramidal, brainstem, and peripheral nerves may all play a role in the neurodegeneration seen in AT, as neurologists have noticed for some time.

In our study 83.33% of patients showed normal choline, creatine and NAA, preserved normal CHO/Cr and CHO/NAA ratios, no lipid and lactate peaks, absent alanine and absent myoinostol and succilloinositol peaks. While, 16.66% of patients with AT showed increased choline with mild reduction of creatine and NAA, increased CHO/Cr and CHO/NAA ratio, no lipid and lactate peaks, absence of alanine and presence of myoinostol and succilloinositol peaks. Conversely to our study, **Wallis *et al.*** [(15)] found that patients with ataxia telengectesia did not have metabolic abnormalities in their basal ganglia or parietooccipital white matter (WM). An increase in the Cho signal could be seen in the cerebellum's dentate nucleus, which displayed lower NAA/Cho but elevated Cho/Cr. Vermal quantitative analysis, on the other hand, showed a significant decrease in NAA and Cho.

In our study, there was statistically non-significant relation between total SARA score and MRI findings of the studied patients. Patients with findings suggestive of cerebellar atrophy had higher total score. There was statistically significant relation between total SARA score and MRS findings. Patients with normal MRS have significantly lower total score.

As there were few articles correlating the MRS with AT and only describe the relation between MRS and other ataxias. Conversely to our finding, **Boesch *et al.* [16]** described a lactate peak in the pons of SCA2 patients as well. NAA/Cr and Cho/Cr ratios were decreased, while mI showed high levels in the pons and cerebellum of SCA2 patients In SCA3, there was decreased NAA/Cr and Cho/Cr ratios but to a milder extent compared to SCA2.

CONCLUSION

Functional changes in the brain tissue detected by MRS reflect the severity of Ataxia Telangiectasia manifestation rated by the Scale for the assessment and rating of ataxia (SARA). MRS and SARA are useful tools in studying the causes, clinical picture, diagnosis & treatment of Ataxia Telangiectasia, thus help improving the life quality for its patient. They also show wide success as alternative to the old methods of diagnosis, clinical evaluation, or prediction of the prognosis of the disease.

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