

SARA Scale and Magnetic Resonance Spectroscopy findings in Ataxia Telangiectasia among Children

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Abstract

Ataxia telangiectasia, or AT, is also referred to as Louis-Bar Syndrome. It has also been widely referred to as a genome instability syndrome, a chromosomal instability syndrome, a DNA repair disorder, a DNA damage response (DDR) syndrome and, less commonly, as a neurocutaneous syndrome. AT was given its commonly used name by Elena Boder and Robert P. Sedgwick, who described a familial syndrome of progressive cerebellar ataxia, oculocutaneous telangiectasia and frequent pulmonary infection. SARA is a clinical scale developed by Schmitz-Hübsch et al which assesses a range of different impairments in cerebellar ataxia. Schmitz-Hübsch et al developed the Scale for the Assessment and Rating of Ataxia (SARA) as an alternative to The International Cooperative Ataxia Rating Scale (ICARS). The daily use of ICARS scale in ataxic patients is difficult due to its many assessment items. This new assessment tool has fewer assessment items than the ICARS and therefore has the advantage of easier daily assessment of ataxia.

Keywords: Ataxia Telangiectasia, Magnetic Resonance Spectroscopy

Definition of AT:

AT is an autosomal recessive cerebellar ataxia. AT is characterized by progressive cerebellar degeneration, telangiectasia, immunodeficiency, recurrent sinopulmonary infections, radiation sensitivity, premature aging, and a predisposition to cancer development, especially of lymphoid origin. Other abnormalities include poor growth, gonadal atrophy, delayed pubertal development and insulin resistant diabetes. It is important to note that AT is a complex disease and not all people have the same clinical

presentation, constellation of symptoms and/or laboratory findings (e.g., telangiectasia are not present in all individuals with AT). (1)

Epidemiology of AT:

The prevalence is estimated to be $<1-9/100,000$, although incidences as high as 1 in 40,000 and as low as approximately 1 in 300,000 have been reported. With the exception of consanguineous populations, individuals of all races and ethnicities are affected equally by AT. (2)

Clinical description of AT:

Because not all children develop in the same manner or at the same rate, the diagnosis of AT may not be made until the early school years when the neurologic symptoms (impaired gait, hand incoordination, abnormal eye movements), and the telangiectasia appear or become worse. We utilize the terms “classic” and “mild” to distinguish the two different, but broadly recognized, clinical presentations of AT. People with mild AT present with less severe, later onset manifestations associated with longer survival. (2)

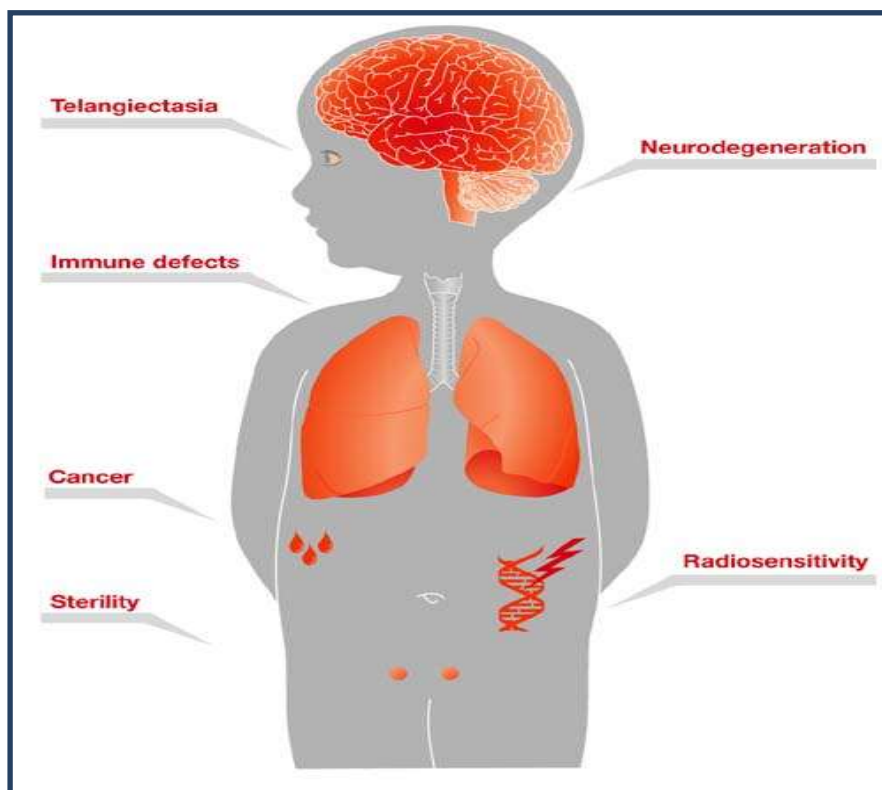


Figure (1): Clinical presentation of AT. (2)

✚ Ataxia and other neurological manifestations:

In the classic presentation of the disease, ataxia first appears during the toddler stage when children begin to sit and walk. Children with AT often start walking at a normal age but then fail to improve much from their initial wobbly gait. Often, they have problems standing or sitting still and tend to sway slowly from side to side or backwards. Because most children with classic AT have stable neurologic symptoms for the first 4–5 years of life, they initially may be labelled as having “ataxic cerebral palsy”, but the existence of such a syndrome is nosologically unclear. (3)

In primary school years, walking becomes more difficult, and children will use doorways and walls for support. Children with AT often run or walk quickly, and do so with a curiously narrow stance, in deference to walking more carefully and slowly. Around the beginning of their second decade children with classic AT start using a wheelchair in the community setting. (2)

Among the scales for ataxia, the International Cooperative Ataxia Rating Scale (ICARS) is widely used as a tool to evaluate the severity and treatment efficacy. Consisting of 19 sub-items divided into 4 subscales, various ataxic symptoms can be assessed comprehensively with ICARS. However, its clinical utility is questionable because of the prolonged duration to complete the test and for this defect, there was a great attention to develop new scales. (4)

SARA scale:

SARA is a clinical scale developed by Schmitz-Hübisch et al which assesses a range of different impairments in cerebellar ataxia. Schmitz-Hübisch et al developed the Scale for the Assessment and Rating of Ataxia (SARA) as an alternative to The International Cooperative Ataxia Rating Scale (ICARS). The daily use of ICARS scale in ataxic patients is difficult due to its many assessment items. This new assessment tool has fewer assessment items than the ICARS and therefore has the advantage of easier daily assessment of ataxia. (5)

The SARA is a tool for assessing ataxia. It has eight categories with accumulative score ranging from 0 (no ataxia) to 40 (most severe ataxia). When completing the

outcome measure each category is assessed and scored accordingly. Scores for the eight items range as follows:

- 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).
- Heel-shin slide (0-4 points). **(5)**

Once each of the 8 categories have been assessed, the total is calculated to determine the severity of ataxia. For motor activities of the four extremities (items 5-8), assessments are performed bilaterally, and the mean values are used to obtain the total score. **(5)**

MRI in AT

The most common neuropathological alterations in AT occurred in the cerebellum, including atrophy of the hemispheres, vermis, and may involve the dentate nucleus. This indicates loss of Purkinje and granule cells from the cerebellar cortex. The presence of basket cells represent that Purkinje cells are present initially but deteriorate during disease progression. Imaging studies of patients with AT have confirmed these pathological criteria. Other frequent signs included hypoplasia of the inferior vermis and a large cisterna magna. **(6)**

AT patient show progressive cerebellar volume loss in children and young people compared to a small linear volume increase in healthy people. The divergence is most marked for total cerebellar volume, cerebellar grey matter volumes and superior vermian lobule volumes, but divergence was identified for all cerebellar sub-regions. cerebellar atrophy can be difficultly detected by visual inspection of diagnostic MRI scans in the first few years of life for children subsequently diagnosed as AT, and this may lead to delay in diagnosis of AT. **(7)**

Although it is surprising that cerebellar atrophy is not the strongest correlate of neurological dysfunction, there are potential explanations. fractional 4th ventricular volume increased significantly with age in the AT individual, which is likely to be dominated by atrophy of surrounding cerebellar structures involving the vermis, cerebellar peduncles, but could also capture subtle atrophy of the dorsal pons, medulla and midbrain. Significant elevation of cerebellar white matter ADC in childhood AT and profound changes in cerebellar metabolite levels, independent of age and cerebellar volume. ADC provides an index of water mobility, and elevation indicates pathological changes in tissue ultrastructure or high tissue water content. elevated mean diffusivity, a diffusion tensor imaging derived metric related to ADC, in the left cerebellar hemispheric white matter and right superior cerebellar lobule of 11 people with AT, confirm that. (8) This group suggested that loss of white matter integrity extends beyond the cerebellum, with diffusion metrics revealed degeneration along corticomotor, corticospinal and somatosensory pathways. (8)

Magnetic Resonance Spectroscopy (MRS) in Ataxias:

Despite technical challenges of magnetic resonance spectroscopy (MRS) in the cerebellum and brainstem, MRS has been shown to be sensitive to neurochemical alterations in various ataxias. Namely, early neurochemical abnormalities have been detected by MRS in ataxias prior to the structural atrophy detectable by conventional MRI and prior to symptoms. Correlations with clinical status and pathological severity were demonstrated in clinical and animal model studies, respectively. (9)

MRS was also shown to distinguish different ataxia subtypes, with potential utility in differential diagnosis, especially valuable for sporadic ataxias in the absence of genetic testing. Finally, a few studies have utilized MRS for treatment monitoring in clinical trials of recessive ataxias, and a great need exists in this area for all degenerative ataxias. More longitudinal investigations and standardization of advanced MRS methodology for multi-site trials will be critical in this respect. (9)

➤ Potential clinical utility of MRS:

In vivo proton magnetic resonance spectroscopy (H MRS) enables non-invasive quantification of endogenous metabolites that exist at millimolar concentrations in selected tissue volumes and thereby provides biochemical information that is not available from conventional structural MRI. **(10)**

Specifically, H MRS may provide insight into neuronal viability (N-acetyl aspartate, NAA), cellular proliferation or membrane turnover (choline-containing compounds, tCho), glial activation (myo- inositol, mIns), neurotransmitter activity (glutamate, glutamine, γ -aminobutyric acid (GABA)), oxidative stress (glutathione, vitamin C), and energy metabolism (creatine, phosphocreatine, glucose, lactate). **(10)**

Since biochemical abnormalities precede the ultimate demise of neuronal populations in neurodegenerative diseases such as hereditary and sporadic degenerative ataxias, a primary potential clinical utility of MRS in ataxias is the early detection of neurochemical abnormalities prior to the cerebellar and brainstem atrophy detectable by conventional MRI. This may enable detection of disease onset in mutation carriers of hereditary ataxias and allow the timely administration of potential neuroprotective therapies. **(11)**

Along the same lines, MRS may help with monitoring of the effects of potential therapies in degenerative ataxias. While ataxias are currently untreatable, neuronal, and motor dysfunction has been shown to be reversible in mouse models. Furthermore, advances in understanding of molecular mechanisms of common ataxias have raised a realistic hope for the development of effective therapeutic interventions. **(11)**

However, assessing whether therapies can abate progression of neurodegenerative diseases is challenging because of their slow progression and phenotypic variability, which in turn necessitate long clinical trials with large sample sizes, a particular challenge for rare diseases like ataxias. **(12)**

MRS has the potential to directly assess disease-modifying effects of therapeutic interventions in the brain and to gauge their effectiveness quickly and objectively. Another area where MRS may have clinical impact in ataxias is differential diagnosis. While the definitive diagnosis in hereditary ataxias will always rely on genetic testing, distinguishing

ataxias by non-invasive imaging has been a long-term interest in the ataxia field because such biomarkers could guide genetic testing in the absence of family history and help with diagnosing sporadic ataxias. (12)

➤ Overview of MRS findings in Ataxias:

Prior to the identification of the causative genes for many hereditary ataxias, studies classified ataxias using either clinically defined criteria or imaging-based criteria, such as olivopontocerebellar atrophy (OPCA) and cerebellar cortical atrophy (CCA). Considering the pathological heterogeneity between different ataxia subtypes grouped under these classifications, below we will primarily focus on reports of genetically defined ataxias, as well as sporadic ataxias. (9)

✚ Recessively Inherited Ataxias:

A number of MRS studies in autosomal recessive cerebellar ataxias have been reported. Most of these studies have been performed in patients with FRDA, the most common form of recessive ataxia. A few additional studies have been reported in AT, AOA2, and ARSACS. Many of these studies show significant neurochemical differences between patients and controls, with a decrease in total NAA (NAA β N-acetylaspartylglutamate, tNAA) and an increase in mIns being the most common findings. (9)

✚ AtaxiATelangiectasia (AT) and AtaxiATelangiectasia-Like Disorder (ATLD):

One study reported decreased tNAA/tCho and increased tCho/tCr in the cerebellar white matter of patients with AT compared to controls, with no change in tNAA/ tCr. This suggests elevated tCho, although the data are also consistent with a simultaneous decrease in tCr and tNAA. Proton MRS using water as an internal concentration reference would permit discrimination between those two possibilities. (9)

✚ Dominantly Inherited Ataxias:

The majority of MRS studies in patients with dominantly inherited ataxias thus far showed a reduction in tNAA or tNAA/tCr at 1.5T, as is common in neurodegenerative diseases. Evidence that these changes are detectable very early in the disease course came from a report of lower tNAA/tCr and tCho/tCr in the pons of carriers of the SCA1 mutation, including two asymptomatic carriers. While metabolite level/ratio alterations are detectable

prior to symptoms, MRS-measured metabolites have also been found to reflect the symptomatic progression in ataxias. **(10)**

Namely, correlations between tNAA and clinical scores were shown in patients with cerebellar degeneration starting with the earliest studies. Correlations were observed between pontine tNAA/tCr and clinical disability in a combined group of patients with OPCA, including SCA1 and SCA2, between pontine tNAA and ataxia scores in SCA1 and between tNAA, tCho, and disease duration in SCA2. **(13)**

Several investigations focused on neurochemical differences between different dominant ataxia subtypes. A pilot study reported lower cerebellar tNAA/tCr and tCho/tCr ratios in SCA2 than SCA6, suggesting a higher degree of neuronal dysfunction or loss in SCA2. This was consistent with a larger study that reported lower cerebellar tNAA/tCr and tCho/tCr ratios in SCA2 than both SCA3 and SCA6. **(13)**

Interestingly, the same ranking was observed in the severity of neurochemical abnormalities and known levels of synaptic loss between SCA1, SCA2, and SCA6, with the most severe involvement in SCA2, followed by SCA1 and SCA6, raising the possibility that neurochemical alterations may reflect synaptic density. The higher data quality and the ability to quantify extended neurochemical profiles also allowed the accurate classification of these dominant ataxias, even SCA1 and SCA2, which has been challenging previously. **(14)**

In SCA1, SCA3, and SCA7, strong correlations were detected between select metabolites (tNAA, mIns, tCr, glutamate) and a validated ataxia score. These neurochemicals also allowed the separation of patients from controls without any overlap, suggesting that high-field MRS may be used for clinical decision making on an individual subject basis. **(14)**

MRS was further used to noninvasively demonstrate the pathological involvement of regions other than the cerebellum and brainstem in dominant ataxias, e.g., the deep cerebral white matter in SCA3 and cerebral cortical and white matter regions in SCA1. Finally, the cerebellar tNAA/tCr ratio was recently shown to accurately predict the age of disease onset in SCA2 and SCA3. **(15)**

Sporadic Ataxias:

MRS studies in sporadic ataxias primarily tested the diagnostic utility of the technique, which may be very valuable in the absence of genetic testing. For example, distinguishing MSA-C from other forms of sporadic cerebellar degeneration is important as prognoses are quite different between these disease entities. An early study reported reductions in cerebral and cerebellar tNAA/tCr in patients with MSA and sporadic CCA and suggested that the two groups could be distinguished based on putaminal tNAA/tCr, which was low only in MSA. (9)

This study also showed significant correlations between the cerebellar tNAA/tCr and a functional ataxia scale and between frontal cortex tNAA/tCr and mini-mental state examination scores in both groups. Others attempted to distinguish MSA-C from MSA-P. tNAA/tCr was lower than controls both in the pons and putamen in MSA-P, while only the pontine tNAA/tCr was altered in MSA-C. In addition, tNAA/tCr alterations were present prior to ataxic symptoms and MRI abnormalities in this study. (9)

Due to the similarities in clinical presentation and ages of onset, distinguishing MSA-C from the SCAs using neuroimaging is also expected to be valuable in the clinic. Among the most common SCAs, SCA2 has the most similar cerebellar metabolite ratios (tNAA/tCr and tCho/tCr) to those in MSA-C, and metabolite ratios have been largely insufficient to distinguish MSA-C from SCA2. (13)

Rater: _____ date: _____ patient: _____

Scale for the assessment and rating of ataxia (SARA)

<p>1) Gait</p> <p>Proband is asked (1) to walk at a safe distance parallel to a wall including a half-turn (turn around to face the opposite direction of gait) and (2) to walk in tandem (heels to toes) without support.</p> <ul style="list-style-type: none"> 0 Normal, no difficulties in walking, turning and walking tandem (up to one misstep allowed) 1 Slight difficulties, only visible when walking 10 consecutive steps in tandem 2 Clearly abnormal, tandem walking >10 steps not possible 3 Considerable staggering, difficulties in half-turn, but without support 4 Marked staggering, intermittent support of the wall required 5 Severe staggering, permanent support of one stick or light support by one arm required 6 Walking > 10 m only with strong support (two special sticks or stroller or accompanying person) 7 Walking < 10 m only with strong support (two special sticks or stroller or accompanying person) 8 Unable to walk, even supported 	<p>2) Stance</p> <p>Proband is asked to stand (1) in natural position, (2) with feet together in parallel (big toes touching each other) and (3) in tandem (both feet on one line, no space between heel and toe). Proband does not wear shoes, eyes are open. For each condition, three trials are allowed. Best trial is rated.</p> <ul style="list-style-type: none"> 0 Normal, able to stand in tandem for > 10 s 1 Able to stand with feet together without sway, but not in tandem for > 10s 2 Able to stand with feet together for > 10 s, but only with sway 3 Able to stand for > 10 s without support in natural position, but not with feet together 4 Able to stand for >10 s in natural position only with intermittent support 5 Able to stand >10 s in natural position only with constant support of one arm 6 Unable to stand for >10 s even with constant support of one arm
<p>Score</p>	<p>Score</p>
<p>3) Sitting</p> <p>Proband is asked to sit on an examination bed without support of feet, eyes open and arms outstretched to the front.</p> <ul style="list-style-type: none"> 0 Normal, no difficulties sitting >10 sec 1 Slight difficulties, intermittent sway 2 Constant sway, but able to sit > 10 s without support 3 Able to sit for > 10 s only with intermittent support 4 Unable to sit for >10 s without continuous support 	<p>4) Speech disturbance</p> <p>Speech is assessed during normal conversation.</p> <ul style="list-style-type: none"> 0 Normal 1 Suggestion of speech disturbance 2 Impaired speech, but easy to understand 3 Occasional words difficult to understand 4 Many words difficult to understand 5 Only single words understandable 6 Speech unintelligible / anarthria
<p>Score</p>	<p>Score</p>

Figure (2) : SARA scale (part 1). (5)

Rater: _____ date: _____ patient: _____

5) Finger chase Rated separately for each side Proband sits comfortably. If necessary, support of feet and trunk is allowed. Examiner sits in front of proband and performs 5 consecutive sudden and fast pointing movements in unpredictable directions in a frontal plane, at about 50 % of proband's reach. Movements have an amplitude of 30 cm and a frequency of 1 movement every 2 s. Proband is asked to follow the movements with his index finger, as fast and precisely as possible. Average performance of last 3 movements is rated.			6) Nose-finger test Rated separately for each side Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to point repeatedly with his index finger from his nose to examiner's finger which is in front of the proband at about 90 % of proband's reach. Movements are performed at moderate speed. Average performance of movements is rated according to the amplitude of the kinetic tremor.		
0 No dysmetria 1 Dysmetria, under/ overshooting target <5 cm 2 Dysmetria, under/ overshooting target < 15 cm 3 Dysmetria, under/ overshooting target > 15 cm 4 Unable to perform 5 pointing movements			0 No tremor 1 Tremor with an amplitude < 2 cm 2 Tremor with an amplitude < 5 cm 3 Tremor with an amplitude > 5 cm 4 Unable to perform 5 pointing movements		
Score	Right	Left	Score	Right	Left
mean of both sides (R+L)/2			mean of both sides (R+L)/2		
7) Fast alternating hand movements Rated separately for each side Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to perform 10 cycles of repetitive alternation of pro- and supinations of the hand on his/her thigh as fast and as precise as possible. Movement is demonstrated by examiner at a speed of approx. 10 cycles within 7 s. Exact times for movement execution have to be taken.			8) Heel-shin slide Rated separately for each side Proband lies on examination bed, without sight of his legs. Proband is asked to lift one leg, point with the heel to the opposite knee, slide down along the shin to the ankle, and lay the leg back on the examination bed. The task is performed 3 times. Slide-down movements should be performed within 1 s. If proband slides down without contact to shin in all three trials, rate 4.		
0 Normal, no irregularities (performs <10s) 1 Slightly irregular (performs <10s) 2 Clearly irregular, single movements difficult to distinguish or relevant interruptions, but performs <10s 3 Very irregular, single movements difficult to distinguish or relevant interruptions, performs >10s 4 Unable to complete 10 cycles			0 Normal 1 Slightly abnormal, contact to shin maintained 2 Clearly abnormal, goes off shin up to 3 times during 3 cycles 3 Severely abnormal, goes off shin 4 or more times during 3 cycles 4 Unable to perform the task		
Score	Right	Left	Score	Right	Left
mean of both sides (R+L)/2			mean of both sides (R+L) / 2		

Figure (3) : SARA scale (part 2). (5)

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