Cerebellum
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REVIEW

Radiological Imaging in Ataxia Telangiectasia: a Review

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Abstract The human genetic disorder ataxia telangiectasia (A-T) is characterised by neurodegeneration, immunodeficiency, radiosensitivity, cell cycle checkpoint defects, genomic instability and cancer predisposition. Progressive cerebellar ataxia represents the most debilitating aspect of this disorder. At present, there is no therapy available to cure or prevent the progressive symptoms of A-T. While it is possible to alleviate some of the symptoms associated with immunodeficiency and deficient lung function, neither the predisposition to cancer nor the progressive neurodegeneration can be prevented. Significant effort has focused on improving our understanding of various clinical, genetic and immunological aspects of A-T; however, little attention has been directed towards identifying altered brain structure and function using MRI. To date, most imaging studies have reported radiological anomalies in A-T. This review outlines the clinical and biological features of A-T along with known radiological imaging anomalies. In addition, we briefly discuss the advent of high-resolution MRI in conjunction with diffusion-weighted imaging, which enables improved investigation of the microstructural tissue environment, giving insight into the loss in integrity of motor networks due to abnormal neurodevelopmental or progressive neurodegenerative processes. Such imaging approaches have yet to be applied in the study of A-T and could provide important new information regarding the relationship between mutation of the ataxia telangiectasia mutated (ATM) gene and the integrity of motor circuitry.

Keywords Ataxia telangiectasia · Cerebellum · Magnetic resonance imaging · Diffusion magnetic resonance imaging

Abbreviations

A-T	Ataxia telangiectasia
dMRI	Diffusion magnetic resonance imaging
DTI	Diffusion tensor imaging
GM	Grey matter
HARDI	High angular resolution diffusion imaging
MRI	Magnetic resonance imaging
WM	White matter

A-T and Genetic Origins

Ataxia telangiectasia (A-T, Louis–Bar syndrome) is an autosomal recessive neurodegenerative disorder that occurs in 1 per 88,000 live births in the USA [1]. In the UK, an estimated fourfold lower incidence of approximately three per million live births has been reported [2]. The disease was first characterised in 1941 [3] and localised to chromosome 11 q22-q23 in 1988 [4]. Multi-system characteristics associated with A-T were subsequently shown to be a result of mutation in a single gene, ATM (ataxia telangiectasia mutated) [5] and

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include progressive cerebellar ataxia, immunodeficiency, sinopulmonary infections, oculocutaneous telangiectasia [6, 7] and elevated serum alpha-fetoprotein levels [8]. The ATM gene encodes for the protein kinase ATM, a key player in the cellular response to double-stranded DNA damage [9] and multiple cell cycle checkpoint pathways [10]. As such, ATM gene mutation is associated with increased radiosensitivity in A-T patients [11–23]. The causes of death in most patients are lymphoreticular malignancy or recurrent chronic respiratory infections [6, 7].

A-T Neuropathology

Since the localisation of the ATM gene to chromosome 11, over 500 different ATM mutations have been identified that give rise to unique A-T case symptoms [24–26]; some of which are characteristic from family to family [27–29]. This genetic variation extends to the neurological symptoms of A-T, which differ on a case-by-case basis and can be grouped by anatomic region. Known neuropathology based on post-mortem studies in A-T is summarised below.

Cerebrum

Anatomical studies in A-T have reported widely distributed cerebral tissue vascular changes. The presence of numerous Lewy bodies and moderate nerve cell loss in the substantia nigra represent part of these changes [29–33]. Haemosiderin scarring in frontal lobe white matter (WM), the parietal area, including the parietal operculum, in the temporal lobe, in the subcortical area of both occipital lobes and capsula externa has been reported [33, 34]. Smaller scarring has been observed in the WM of the precentral and post-central gyrus [34] as well as moderate cortical gliosis of the central and parietal gyri [30]. Lesions within the thalamus have been reported [30, 32]. Basal ganglia pathology in A-T has also been described, particularly glial scarring and demyelination in the frontal plane sections of both basal ganglia hemispheres [34].

Cerebellum

Cerebellar pathology in A-T includes cerebellar atrophy of the frontal and posterior vermis and atrophy of both cerebellar hemispheres, particularly in the middle and superior cerebellar peduncles (brachia pontis and conjunctiva, respectively) [29, 30, 32–40]. On a microscopic scale, the loss of Purkinje cells and loss or reduction of granular cell layers, especially in the anterior cerebellar vermis, is a hallmark feature in A-T [30, 31, 33–36, 39–43]. Abnormal nuclear and dendritic arborisations in Purkinje neurons have also been reported [30, 36]. A number of generalised findings relating to the loss of occipital cortex pyramidal cells, smaller than average dentate nucleus, larger than average inferior olivary nucleus venules, where the inferior olivary nuclei showed nerve cell loss and reduced myelinated fibres in the nervus hypoglossas and enlarged venules in the cerebellar meninges have been described [29–31, 39, 40].

Brainstem

Brainstem abnormalities in A-T are dependent on individual patients and age. In some studies, no brainstem abnormalities were seen [37, 40]. In other cases, glial nodules in pyramidal tracts and the medial lemnisci and gliosed gracile nuclei were observed [36]. Sectional demyelination of the pons and midbrain in the brachia conjunctiva and pontis has also been reported [34]. Other more comprehensive case studies observed atrophy in the rostral mesencephalic nucleus of the trigeminus, poorly pigmented neurons of the locus coeruleus, medial/inferior vestibular nuclei and medullary reticular formation, smaller medullary pyramids with gliosed dorsal portions; and gliosed Goll's and Burdach's nuclei [29, 30, 33]. Other pathological findings include neuroaxonal dystrophy in the medulla oblongata tegmentum, particularly in the gracilis and cuneatus nuclei [31, 39]. Nuclei of the 5th, 6th, 7th and 12th cranial nerves have also been shown to display varying neuronal loss and gliosis [31].

Spinal Cord

Pathology in lower motor neurons of the spinal cord is generally reported in A-T patients that live past their third decade [30, 38, 39]. The earliest study to discuss spinal cord pathology in A-T reported severe spinal dorsal tract demyelination and fibrillary gliosis, especially in the cervical area and the cuneate and gracile fascicle. Proximal spinal root demyelination and fibrosis, focal necroses in the anterior spinal cord and abnormal grey matter (GM) structures in the cervical and lumbar spinal cord have also been recorded [35]. Pallor regions and demyelination in the posterior spinal column has been described, particularly in the fasciculus gracilis, to a lesser degree in the fasciculus cuneatus, in the crossed pyramidal tracts and in dorsal spinocerebellar tracts [29–33, 36–39]. Demyelination of the entire posterior funiculi [34], the fasciculus proprius, the lateral corticospinal tracts [31] and the gliosis of the anterior funiculi has also been recorded [30]. Anterior horn cell degeneration in patients (30–40 years) has also been observed [29–34, 39, 43, 44]. Other affected areas of the spinal cord are the dorsal root ganglia, with morphological and histological abnormalities that differ between individuals [30, 32, 36, 43]. In peripheral nerves, extensive myelin and axon loss has been recorded in the sural, anterior tibial, femoral and sciatic nerves and cervico-brachial and lumbosacral plexus [29, 31].

A-T Neurodegeneration: Oxidative Stress

As mentioned above, neurodegeneration in A-T is highly dependent on the age and individual patient. The primary cause of A-T neurodegeneration is the inability of the ATM protein to regulate oxidative stress levels in the cerebellum, leading to the apoptosis of oxidative stress sensitive Purkinje cells. Early studies using human and rodent models have shown that ATM protein expression is highest in the cerebellum [45, 46], particularly in the cytoplasm of Purkinje cells [47]. Recent studies have shown ATM protein localisation to cerebellar Purkinje neuron nuclei in human brain tissue [48].

The earliest paper to report reactive oxygen species involvement in A-T describes G2 phase sensitivity to hydrogen peroxide in A-T cells [49]. The ATM protein is a sensor of DNA damage and a regulator of cellular homeostasis under oxidative stress [9, 50]; thus, ATM deficiency causes the buildup of reactive oxygen species intermediates and Purkinje cell apoptosis due to these intermediates [51–54]. Purkinje cell degeneration is also attributed to the overproduction of nitric oxide (NO), which is a neurotransmitter to the cells [51]. NO can react with the high levels of superoxide anions in ATM deficient cerebella [46] to form the strong oxidant peroxynitrite [51, 55, 56], leading to an increase in cerebellar oxidative species and subsequent DNA and protein damage to Purkinje cells.

To manage A-T neurodegenerative symptoms, investigation into therapies focusing on the use of the glucocorticoids dexamethasone and betamethasone have been undertaken [54, 57–64]. In mouse models, dexamethasone has been found to inhibit redox activities in both thymocytes and splenocytes with or without *Atm*, arrest the cell cycle of *Atm* knockout thymic lymphoma cells at the G1 phase and cause apoptosis in ATM knockout thymocytes, preventing thymic lymphoma in mice [65–68]. Of the two glucocorticoids, betamethasone has undergone preliminary clinical testing in A-T. In an early study, betamethasone was reported to improve neurological symptoms in a child diagnosed with A-T, 2 to 3 days after initial treatment. This improvement continued 2 weeks into treatment, where ataxic stance and gait was reduced and head and neck control as well as skilled movement control was improved. At 4 weeks, the only adverse side effects were increased appetite, body weight and moon face; however, after 4 weeks, no beneficial effects were observed. At this point, drug therapy was switched to the glucocorticoid methylprednisolone, and after 6 months without therapy, the child showcased severe impairment of the central nervous system. The serum α-fetoprotein level was unchanged during and after treatment [69]. An extension of this study using six patients produced similar results [70]. A separate multi-center, double-blind, randomised, placebo-controlled crossover trial using 13 A-T affected children and oral betamethasone and placebo also yielded a reduction of ataxia symptoms among A-T subjects [71]. For these studies, cerebellar improvement and antioxidant increase was found to be drug dependent [71, 72]. Lower doses of betamethasone (30 % of what is given to patients) were found to be effective and result in milder steroid side effects; however, α-fetoprotein levels do not change [73].

These preliminary studies have demonstrated that improved response from betamethasone is associated with age, with younger patients showing better resolution of the clinical ataxia measures [70]. These findings suggest that a threshold level of cerebellar degeneration may be a prerequisite to successful steroid therapy in A-T [74, 75]. Such a threshold level may be determined using non-invasive imaging with MRI, especially diffusion-weighted imaging, which enable the extent of degeneration of cerebellar–corticomotor pathways to be quantitatively assessed in a number of ataxic conditions [76–83].

Interestingly, a recent fMRI pilot study where A-T patients received a 10-day cycle of oral betamethasone has shown increased activation within corticomotor regions after treatment using simple motor tasks [84]. This preliminary work suggests that steroid treatment could improve motor performance, facilitating cortical compensatory mechanisms. Importantly, this pilot study gives evidence that non-invasive fMRI studies may be useful to monitor treatment effects.

Summary of Radiological Findings in A-T

Early work in understanding radiological changes associated with A-T involved the use of CT to detect cerebellar atrophy [85–88]. These studies reported no cerebral, pons or cerebellar vermis atrophy [89]; however, brainstem calcifications were observed in patients in their fourth decade [88]. Despite the high spatial resolution, such findings highlight the significant challenges of using CT to delineate subtle neuropathological changes associated with A-T (reviewed in [90]). Limits to radiation dosimetry measures also impact on the use of CT to study A-T. MRI is the preferred imaging modality due to its high spatial resolution, superior soft tissue contrast affording exquisite detail of anatomical structures and lack of radiation. In addition, MRI can be employed in a serial fashion to not only target morphological changes but also measure physiologic parameters, including cellular diffusion [91, 92] and permeability [93], making this modality ideally useful for neurological research.

To date, only 18 MRI studies focusing on A-T patients have been reported in the English language [26, 84, 94–109]. Further details of these studies are summarised in Table 1. In general, MRI findings in A-T patients have reported cerebellar atrophy, specifically of superior cerebellar hemispheres or vermis, inferior cerebellar vermis hypoplasia, enlarged fourth ventricles and large cisterna magna, with variations among individuals [26, 94–96, 99, 101, 102, 104, 107, 109]. These

Table 1 Summary of CT/MRI studies in A-T

Reference	Image type (CT/T1/T2/fMRI)	Age range (years)	Gender (M/F)	Major findings
Huang and colleagues [26]	N/A but possibly CT/T1	4–14	2/6	Findings: cerebellar atrophy via CT and MRI examinations
Quarantelli and colleagues [84]	T1/T2/fMRI	7–17	2/2[a]	Aim[c]: to test if steroid (betamethasone) induced motor performance changes in A-T is associated with fMRI modifications Findings: increase in the number of activated voxels within the motor cortex under the on-therapy condition compared with the cortical activity under baseline condition in 2 patients
Demaerel and colleagues [94]	CT/T1/T2	3–22	3/2	Findings: cerebellar atrophy in 4 patients, with discrete calcification on CT in the lentiform nuclei, WM low density and cortical thickening consistent with pachygyria. Cerebellar atrophy detected in MRI in one patient
Farina and colleagues [95]	CT/T1/T2	4–22	6/6[b]	Findings: cerebellar atrophy, decreased thickness of superior cortex of cerebellar hemispheres, hypoplasia of inferior vermis and large cisterna magna observed in A-T patients
Sardanelli and colleagues [96]	T1/T2/T2[a]	9–28	5/0	Findings: vermian atrophy, enlarged fourth ventricles and cisterna magna noted in all patients. Four patients had cerebellar hemisphere atrophy and two had enlarged infracerebellar subarachnoid spaces. Diffuse symmetrical high signal seen in central WM of cerebral hemispheres on T2- weighted images of oldest patient. Brainstem and basal ganglia changes not seen
Ciemins and colleagues [97]	T1/T2	31	0/1	Findings: multiple small foci of decreased WM observed
Opeskin and colleagues [98]	T1/T2	34	1/0	Findings: gross cerebellar atrophy, lesions consistent with vascular malformations in cerebral WM with surrounding abnormal tissue consistent with gliosis found. MRI scans 6 months apart from the age of 32 years showed progression of lesions
Kamiya and colleagues [99]	T1/T2	24	1/0	Findings: coagulated necrosis of brain WM and vascular abnormalities in the brain parenchyma found.
Huang and colleagues [100]	CT/T1/T2	7–8	1/1	Findings: in male A-T subject, MRI and CT revealed no abnormalities. Brain MR in female A-T subject revealed cerebellar atrophy
Tavani and colleagues [101]	T1/T2	2–12; eldest, 35 and 38	10/9	Findings: 2-year-old was normal. In the five next youngest patients (3–7 years), lateral cerebellar and superior vermis atrophy was seen. Five patients who were unable to walk had diffuse atrophy in both the vermis and cerebellar hemispheres
Firat and colleagues [102]	T1/T2	9–13	5/1	Findings: clear differences in cerebellar atrophy in A-T patients compared to controls. In early MRI diagnosis of A-T, diffuse atrophy of the superior cerebellar cortex was found. Cerebellar mean apparent diffusion coefficient (ADC) values of patients and controls were statistically different ($p<0.011$–0.0001)
Lin and colleagues [103]	T2/MR spectroscopy	9–27	3/5	Aim[c]: to measure regional metabolite levels in the posterior fossa and basal ganglia of A-T patients

Table 1 (continued)

Reference	Image type (CT/T1/T2/fMRI)	Age range (years)	Gender (M/F)	Major findings
				Findings: in A-T, there was loss of all metabolites in the cerebellar vermis and decreased metabolites in the cerebellar hemispheres. No abnormalities in the basal ganglia were seen
Wallis and colleagues [104]	T1/T2/T2[a]/MR spectroscopy	23–47	7/5	Findings: cerebellar atrophy of vermis and hemispheres was observed in all A-T patients. Cerebellar analysis revealed significantly lower NAA/Cho and higher Cho/Cr ratios in A-T compared to controls (*N*-acetylaspartate (NAA), choline (Cho), and creatine (Cr))
Habek and colleagues [105]	T1/T2/T2[a]	34	0/1	Findings: extensive and diffuse WM demyelination, T1 and T2 hypointense lesions, T1 hypointense but T2 hyperintense lesions and dilated telangiectases seen in A-T
Kieslich and colleagues [106]	T1/T2	8–26	6/5	Findings: marked hyperintense lesions in the cerebral WM of T2-weighted MR images and spinal atrophy and MRI abnormalities of the basal ganglia in one patient were found. MRI in patients with normal IGF-1 levels showed cerebellar lesions in four patients and spinal atrophy in only two patients. No affection was seen of the cerebral WM or basal ganglia in this group
Al-Maawali and colleagues [107]	T1/T2	Age of onset, 1–3	N/A	Findings: isolated cerebellar atrophy in A-T MRI scans, with no extracerebellar findings
Chung and colleagues [108]	T2	4	0/1	Findings: MRI scans showed leukoencephalopathy which matches leukodystrophy, a neuroimaging feature of A-T not described before
Lin and colleagues [109]	T1/T2	19–34	4/6	Findings: manifest cerebellar atrophy was seen in A-T; supratentorial brain showed no sign of volume loss. Intracerebral telangiectasia with multiple punctate haemosiderin deposits were identified in 60 % of subjects

[a] Two patients were excluded because of insufficient compliance [84]

[b] One subject was a heterozygote parent [95]

[c] Aims are listed in studies that were not entirely anatomy-based

findings support post-mortem clinical observations, with slight differences in anatomical detail. As mentioned previously, post-mortem studies have reported specific cerebellar pathology in the frontal and posterior vermis, in the middle and superior cerebellar peduncles of both cerebellar hemispheres [29, 30, 32–40] and other generalised findings (see "Cerebellum" section) [29–31, 39, 40]. These variations in post-mortem and radiological findings can be attributed to the genetic variation of ATM mutations in the A-T population, which further extend to the disease neuropathology such that A-T symptoms in the same anatomic region differ on a case-by-case basis. In addition, radiological and post-mortem studies involved patients at different progressive stages of the disease; thus, differences in A-T neuropathology between the two study modalities can be expected.

T1- and T2-weighted images have shown multiple WM small foci of signal hypointensities in A-T patients, which were hypothesised to be haemosiderin areas related to haemorrhage from capillary telangiectasias or gliovascular nodules [97]. Asymptomatic supratentorial vascular abnormalities in the cerebrum have also been reported in a recent study using 10 adult A-T patients, where intracerebral telangiectasia with multiple punctate haemosiderin deposits were identified in 60 % of the imaged patients [109]. These more recent findings reflect post-mortem observations of cerebral pathology in A-T [33, 34] with slight pathological differences due to individual patient differences and differences in progressive stage of disease.

The number of published MRI studies in A-T is limited; however, it can be seen that abnormal radiological findings

reported from MRI were subtle for A-T patients until age 10; after which, cerebellar atrophy becomes more evident [101]. However substantial variation in cerebellar atrophy with age does exist as evidenced in Fig. 1. In this case, significant cerebellar atrophy is clearly present in a 7-year-old child with A-T. Again, these observations may differ between case studies and between different A-T cohorts.

The evolution of neuropathological changes in very young children with A-T is not well understood. One case study reported MRI findings of a 4-year-old child who was scanned at 17 months of age. The early images showed leukoencephalopathy compatible with leukodystrophy, a neuroimaging finding that has not been described in A-T [108]. This eludes to the possibility of diffuse WM signal intensity on T2-weighted MRI [110], which indicates progressive demyelination may occur in the early stages of A-T. The specificity of this finding has yet to be established. MRI scans in older patients in their second and third decade also show varied findings in the cerebellar and cerebral lesion progression, such as corpora amylacea [98], diffuse symmetrical high signal in the central WM of cerebral hemispheres on T2-weighted images [96], scattered calcified deposits in the cerebrum WM and space occupying lesions in the right frontal lobe WM and left paraventricular WM [99, 105]. Both of these lesions were displayed with low intensity on T1-weighted images and high intensity on T2-weighted images [99]. General spinal atrophy and abnormalities in the basal ganglia have also been reported in older A-T patients [106], supporting post-mortem spinal study findings in older A-T patients, but lacking specific anatomical detail (see "Spinal Cord" section).

Discussion

Very few studies have focused on reporting radiological findings in A-T [84, 94–99, 101–108]. Of these, studies using standard T1- and T2-weighted MRI sequences have consistently shown diffuse cerebellar atrophy, predominantly within the vermis and cerebellar hemispheres. This reflects the loss of Purkinje cells on a histological level, which is a well-established neuropathological hallmark of A-T. Foci of T2-weighted WM hypo- and hyper-intensity have also been observed and attributed to capillary telangiectasia and focal extracerebellar demyelination [97].

While these morphological studies have been useful from a radiological perspective, they provide limited information regarding the association between neurodegeneration and the loss in integrity of neural motor networks. A growing body of work has demonstrated that diffusion-weighted MRI (dMRI), particularly diffusion tensor imaging (DTI), allows a more accurate depiction of the integrity of brain and brainstem structures than that afforded by standard MRI [111].

An extension of dMRI is the use of fibre tracking to delineate WM fibre bundles in the brain. The advantage of this approach is that the integrity of specific WM tracts in conjunction with the connectivity of pathways linking multiple brain regions can be assessed [112, 113]. Such technology has been applied to study cerebellar–corticomotor networks in a number of ataxic conditions [76–83]. A recent study in particular has observed cerebello-cerebral WM connectivity disruptions in Friedreich's ataxia with diffusion MRI, tractography and super-resolution track density imaging, which has explained some of the non-ataxic symptoms observed with this disease [114]. To date, there are no published studies investigating degeneration of cerebellar–corticomotor tracts using WM fibre tracking in A-T. Future work using this modality needs to be directed towards understanding the spatial extent of degeneration along each WM pathway, specifically in terms of the connectivity between the cerebellum and cerebrum, to ascertain whether degeneration occurs predominately within the cerebellum and propagates to cerebral regions or occurs along the entire length of the cortico-cerebellar motor pathway. Such studies are urgently required to fully understand the impact of mutation of the ATM gene and loss in connectivity of motor circuits in A-T.

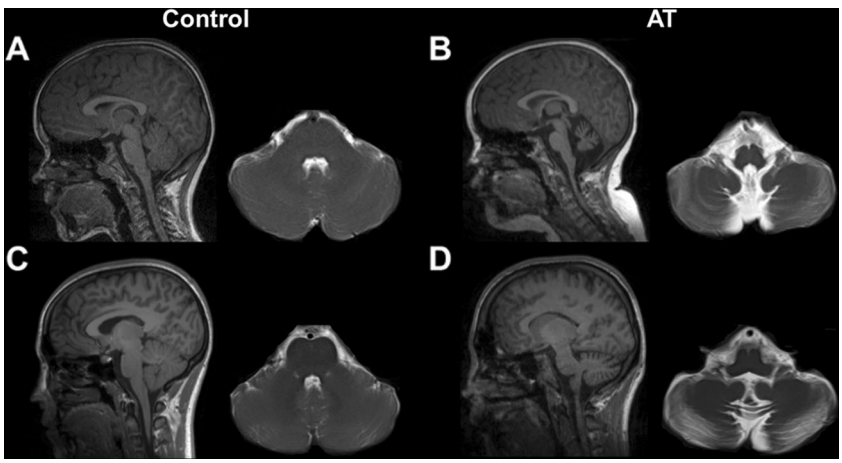

Fig. 1 Age-matched sagittal T1 and axial T2 MRI scans acquired from control (**a**, **c**) and A-T patients (**b**, **d**). The representative images have been acquired from 7- (**a**, **b**) and 23-year-old participants (**c**, **d**). The A-T images show marked cerebellar atrophy with involvement of both hemispheres including the cerebellar vermis

Future studies should also investigate the degeneration of motor pathways involving subcortical structures such as the basal ganglia, which are known to be involved with motor disorders. Although basal ganglia pathology has been associated with mutation of the ATM gene [34], it is currently not known whether striatal–corticomotor pathways are affected in A-T. The integrity of such motor networks is of interest due to a recent study reporting improved neurological measures in A-T patients after treatment with amantadine sulphate [115]. Although the mechanism of amantadine is not well understood, it is believed to act on striatal dopaminergic systems [116, 117]. Future work should also focus on the relationship between clinical measures and the integrity of motor pathways to develop useful biomarkers for monitoring disease progression and assessing the efficacy of new therapies.

Our understanding of the very early neuropathological changes in A-T is limited. Imaging data from infants with A-T is extremely difficult due to delayed onset of clinical phenotypes, and thus, we can only speculate on the integrity of the WM and GM areas, particularly those associated with the cerebellum, which may be compromised at the very early stages of development. Obtaining imaging data from an infant cohort would be extremely beneficial but rather challenging due to the difficulty and complexity of gaining an early diagnosis of A-T. Nonetheless, such information may shed light on the neurodevelopmental origins of A-T.

Conclusion

The various clinical, genetic and immunological aspects of A-T have been reported extensively in past literature, with imaging studies in A-T using CT and MRI to report predominately radiological anomalies. Little attention has been directed towards identifying altered brain structure and function using dMRI, and as such, there are no published studies investigating degeneration of cerebellar–corticomotor tracts using WM fibre tracking in A-T to date. Future work in A-T using dMRI will assist in understanding the spatial extent of degeneration along each WM pathway, specifically the connectivity between the cerebellum and cerebrum, to ascertain whether degeneration occurs predominately within the cerebellum and propagates to cerebral regions or occurs along the entire length of the cortico-cerebellar motor pathway. Such studies are a key first step to fully understand the impact of mutation of the ATM gene and loss in connectivity of motor circuits in A-T.

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