Whole-body MRI for cancer surveillance in children and young people with Ataxia Telangiectasia: Protocol for mixed methods cross-sectional interventional feasibility study

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Abstract

Background/objectives: Ataxia Telangiectasia (A-T) is a complex inherited disease associated with an increased risk of malignancy. Surveillance guidelines have demonstrated significant health benefits in other cancer predisposition syndromes but evidence-based guidelines for cancer surveillance in A-T are lacking. This study will establish technical feasibility of whole-body MRI (WBMRI) for cancer surveillance in children and young people with A-T and assess the psychological impact on participants and their families in response to participating in a cancer surveillance programme.

Methods: In this mixed methods feasibility study, we aim to recruit 20 children and young people with A-T to undergo a WBMRI scan, which will take approximately 40 minutes. This will be followed by an optional blood test. We will invite all participants with A-T and their family members to semi-structured interviews to assess the experience of participating and their feelings about waiting for, and communication of, the findings of the scan. Feasibility outcomes will include the rate of completion of WBMRI protocol, the duration of the scan tolerated (if not full protocol) and the assessment of the diagnostic image quality. Secondary outcomes will include (i) documentation of number, types and locations of abnormal findings on WBMRI and on blood tests; (ii) rates of recommendations for further investigations based on the WBMRI and/or blood test findings; (iii) assessment of experience and psychological impact on the participants and their families/carers throughout the study.

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Discussion: The results of this feasibility study will inform the design of a prospective trial to establish the efficacy and cost-effectiveness of cancer surveillance in A-T.

Trial Registration: Prospective study registration: ClinicalTrials.gov NCT05252819. Registered 23rd February 2022, https://www.clinicaltrials.gov/study/NCT05252819

Keywords: Ataxia-Telangiectasia, cancer predisposition syndrome, life-limiting disease, psychosocial impact, mixed methods research, Whole-body MRI, cancer surveillance

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Background

Ataxia Telangiectasia (A-T) is an autosomal recessive condition caused by mutations in the ataxia telangiectasia mutated (*ATM*) which is associated with cerebellar neurodegeneration, immunodeficiency and respiratory disease[1–3]. The *ATM* gene product (ATM protein kinase) has roles in double-stranded DNA repair and thus *ATM* variants lead to genomic instability with increased sensitivity to ionising radiation and elevated cancer risk (22-24% cumulative incidence up to age 20 years)[1,3–5]. The leading causes of death in A-T are cancer and lung disease[6,7]. Cancer in A-T has been reported as early as 2 years and the median age of diagnosis is 12.5 years[8,9]

Although the Pediatric Cancer Working Group of the American Association for Cancer Research (AACR) recommends surveillance in cancer predisposition syndromes (CPS) with cancer risk above 5% (up to age 20years)[10], specific evidence-based guidance on cancer surveillance in A-T is lacking[7,11]. The AACR Childhood Cancer Predisposition workshop report states that *'Evidence-based standards for cancer screening do not exist for patients with A-T, particularly in childhood'* and recommends consideration of '*Annual physical exam, complete blood count, and complete metabolic profile including lactate dehydrogenase'*[5(p2)].
Advancements in MRI technology allow whole-body imaging with relatively short acquisition times and provide excellent soft-tissue contrast for lesion detection [12–15]. Whole-body MRI (WBMRI) protocols optimised for cancer detection are now used clinically for diagnosing and monitoring cancers and non-cancer lesions[12–14,16–23], and guidelines for some CPS now include MRI[24–29]. Importantly, this technique avoids ionising radiation, which is important in CPS with radiosensitivity, like A-T[13–15].

People with A-T and their families already have the worry of living with a chronic life-limiting childhood-onset disease with a poor overall prognosis and progressive physical disability[1,3,4]. A cancer surveillance programme could add to this burden with a detrimental effect on both

the child with A-T and their family members. It is recognised that surveillance tests can increase anxiety due to the possibility of finding cancer or other pathologies[14]. Data from screening trials related to other CPS have demonstrated mixed psychosocial effects: although anxiety, depression and cancer worry were reported, overall the levels of satisfaction and acceptability were higher[30–33].

Before addressing the current lack of evidence-based guidelines through a formal prospective trial, we first need to know whether cancer surveillance in children and young people with A-T using WBMRI is feasible and acceptable to the patients and their families. Although studies have reported the use of MRI for targeted imaging of the brain[34] and thoraco-abdominal organs[35] in children with A-T, to our knowledge technical success of whole-body MRI acquisition with diagnostic-quality images in a paediatric A-T population has not been demonstrated. The spectrum of findings (both cancer and non-cancer) which might be detected by WBMRI in a paediatric A-T population is also unknown.

Our recent qualitative study based on interviews of people with A-T and family members identified that cancer surveillance was considered important and valuable because of the potential benefits of early cancer diagnosis but there were concerns that it could lead to heightened anxiety related to the scan procedure and potential for an unexpected cancer diagnosis[36]. Quality-of-life is affected by A-T[37] and thus it is important to include the assessment of the negative impacts on people with A-T and their families resulting from undergoing cancer surveillance using WBMRI in prospective studies.

Methods / Design

Primary aim

- To establish the technical feasibility of WBMRI for cancer surveillance in children and young people with A-T.

Secondary aim

- To establish the prevalence and spectrum of cancer and non-cancer abnormalities detected on WBMRI in this population.
- To establish views of, and psychological impact on, participants and families in response to participating in WBMRI for cancer surveillance.

This study will be a mixed methods feasibility study of children and young people with A-T and their families / guardians. Participants will be recruited through the National Paediatric A-T Clinic held at the Nottingham University Hospitals (City Hospital Campus). They will be invited to undergo a single WBMRI scan in the MRI department at Nottingham University Hospitals (Queen's Medical Centre Campus). Participants will be able to opt to have a blood test that includes putative tumour markers. The WBMRI scan will last approximately 40 minutes and the whole visit will last approximately 2 hours depending on the support / preparation required. A follow-up remote video interview will explore the views of, and psychological impact on, participants and families / guardian in response to participating in whole-body MRI for cancer surveillance. Patient flow through the trial is summarised in figure 1.

Eligibility criteria for participants with A-T

Inclusion criteria

- Confirmed diagnosis of A-T
- Aged 4 to 18 years
- Able to undergo MRI scan without sedation or general anaesthetic, after age-appropriate preparation

- Able to give informed consent (if 16 or older), or have a parent or guardian who is able to give informed consent

Exclusion criteria

- Contra-indication to MRI scan

Consent

The written informed parental / guardian consent (see supplementary materials) will be obtained for all participants aged 4 to 15 years before the participant enters the trial. Participants aged 16 years and above will give written consent for themselves. The Investigator will explain the details of the trial and provide an age-appropriate Participant Information Sheet, ensuring that the participant and parent / guardian has sufficient time to consider participating or not. The Investigator will answer any questions that the participant or parent / guardian has concerning study participation. Children and young people under age 16 years will also be asked for their assent agreeing to participation, in addition to the parent / guardian consent. The consent form includes an opt-in clause to undergo an additional blood test with putative tumour markers (detailed below).

In addition to obtaining informed participant or parent / guardian consent for the child or young person to undergo the WBMRI procedure +/- the blood test, we will also seek consent from the parent or guardian for direct participation in the follow-up interview following the WBMRI scan.

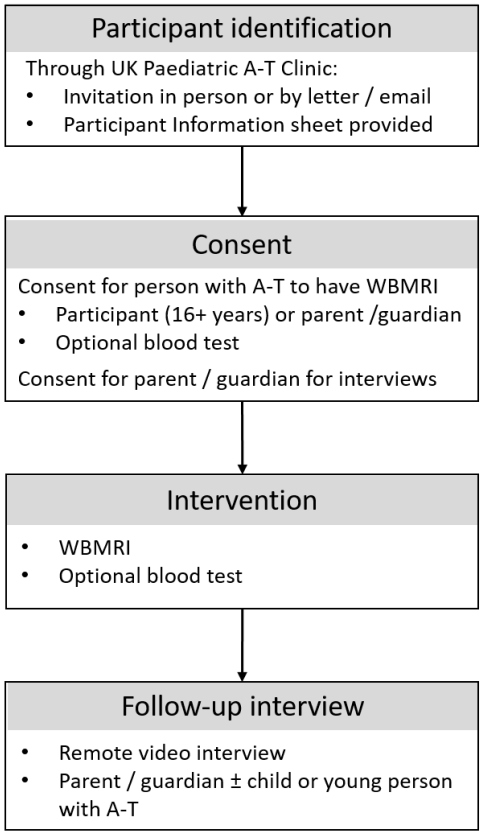


Figure 1: Participant journey flow diagram.

Intervention

The initial assessment will take place in appropriate child-friendly rooms with wheelchair accessibility at the Queen's Medical Centre, Nottingham. In addition to the consenting process mentioned above, the parent / guardian will be asked to complete the MRI safety questionnaire for the child or young person undergoing the WBMRI, and for the parent / guardian accompanying them into the MRI room (if relevant).

Prior to the MRI scan, all participants will be prepared for the scan by an MRI research radiographer who is experienced in preparing children for MRI scans, and participants will be offered the opportunity to undergo a simulated MRI scan in the 'mock' MRI scanner so that they can get used to the environment and have a practice dummy scan.

All participants will undergo WBMRI scanning in a 3T Philips Elition MRI system, with in-built audiovisual entertainment (Ambient Experience, Philips) to improve the experience and provide distraction during the MRI scan. We will offer the option to have a parent or guardian in the room for reassurance. While in the scanner the participant will be able to speak directly to the scanner operator via a two-way intercom inside the scanner. The MRI examination will last approximately 40 minutes with a protocol that includes:

- Whole body MRI imaging that will include diffusion-weighted imaging (DWI), Short Tau Inversion Recovery (STIR) and T_1-weighted anatomical imaging. Acquisition time in total: approximately 30 min.
- Cranial high resolution 3D T_1-weighted anatomical imaging (sagittal acquisition whole brain, MPRAGE). Acquisition time: approximately 4 min.
- Axial Brain T2-weighted anatomical imaging (axial acquisition whole brain). Acquisition time approximately 2 min.

An optional component of the study will be for participants to have a blood sample taken for tests relevant to tumour detection or tumour risk, including full blood count and blood film, alpha fetoprotein, beta human chorionic gonadotropin, lactate dehydrogenase and Epstein-Barr virus serology. The reason for including this component is because these blood tests will be, or are candidates to be, included in the cancer surveillance programme, and hence for the feasibility and participant experience aspects of this study, we believe it is important that they are included. However, we realise that an additional blood test could be distressing for younger children and could reduce recruitment, and hence this an optional component of the study.

The MRI scan will be formally reported by consultant clinical radiologists linked to the study so that if abnormalities are detected, further investigations can be initiated. The (optional) blood test will also be submitted as part of the participant's patient record in case further

investigations are indicated. The report of the MRI scans and results of the blood test, which will be kept in the participants' records within NHS, will go to the relevant clinician in the National Paediatric A-T Clinic at Nottingham University Hospitals. Where the MRI scan or blood test results need acting upon, this clinician will liaise with the participant's own hospital doctor or GP as appropriate by letter or secure NHS email, and will inform the participant and their parent / guardian of the finding using non-medical language, and to explain the next steps. The research team includes two paediatric oncologists, who can provide further advice to clinicians or families on further investigation and management, if required. We will record details of further management; this information is important to allow us to assess the impact of the surveillance programme on participants and the health system.

Immediately following the MRI scan the participants will be asked to rate their comfort and anxiety during MRI scan. The participants and their parents / carers will then be invited to take part in semi-structured interviews approximately 2 to 3 weeks after the scan (i.e. allowing time for reflection on the experience) to explore their perceptions of the preparation for scanning, the experience of scanning and their feelings about the communication of the findings from the scan. These will be conducted online, using videoconferencing software approved by the University of Nottingham such as Microsoft Teams. The interviews/group discussions will allow in-depth exploration of the psychological impacts of participation, and emotions surrounding attendance for the MRI scan / optional blood test, related directly to either the MRI scan or blood test (if applicable), and related to the wait for the result. For those who had abnormalities detected, we will study the impact of being referred for further tests and possibly treatments.

Outcomes

This is a feasibility study and the primary outcomes will be based around: (i) rate of completion of whole-body MRI protocol; (ii) duration of scan tolerated (if not full protocol); (iii) diagnostic image quality assessment.

The secondary outcomes will be: (i) documentation of number, types and locations of abnormal findings on WBMRI and on blood metrics (when available); (ii) rates of recommendations for further investigations based on the WBMRI and/or blood test findings and record of subsequent medical management; (iii) assessment of the psychological impact on the participants and their families/carers throughout the study; (iv) Assessment of participant / parent (carer) experience in the lead up to, during and after the surveillance MRI.

Sample size and justification

As this is a feasibility study, we cannot perform a formal power calculation to inform sample size. The recruitment target of 20 people with A-T and their families / carers to participate is pragmatic, based on our expected recruitment. This target sample size will allow us to show feasibility of the approach and to gain an understanding of the spectrum of findings on whole body MRI in this population.

Data analysis

In view of the small sample size, statistical analysis will be limited to descriptive statistics. Statistical analysis will be performed by the PI (principal investigator) and by the researcher MRI radiographer with support from other co-investigators as required. Statistical Package for the Social Sciences (SPSS) will be the software platform used to conduct the quantitative analysis.

Qualitative data will be evaluated by the health psychologist research assistant and by the researcher MRI radiographer, both supported by the health psychologist professor. Thematic analysis will be the research method used to conduct qualitative analysis.

To address the primary aim, we will record scan completion rate, duration of scan tolerated (if not full protocol), and we will assess the image quality of the MRI scans (evaluated by consultant radiologists as ‘excellent’, ‘good’, ‘acceptable’, ’not good’ and ‘not diagnostic’). We

have established scan completion rate > 50% and image quality between acceptable to excellent in 65% of those completing the scan as successful threshold. We will also report uptake rates for participation amongst those initially approached regarding the study.

To address secondary aims, we will document the number, types and locations of abnormal findings on MRI scans. We will also record the number and types of abnormal findings on blood metrics. The number of recommendations for further investigation based on the MRI scans and/or blood test and the number of subsequent medical management required will also be documented. Finally, we will record participants and parents / carers views and experience in participating in the full study. We have established a positive response / acceptance of >50% as a successful threshold.

Confidentiality and access to data

As this study aims to assess the feasibility of a cancer surveillance programme including obtaining MRI scan data and blood test data, we will not be able to keep all data anonymous in order to facilitate diagnostic evaluation. Therefore, de-anonymised data will become part of the participants' patient records with the NHS to support their usual care. For example, the MRI scan will be requested under the patient's name and will be formally reported by two NHS radiologists so that if abnormalities are detected, further investigations can be made, which may result in treatment according to the clinical judgement of the NHS healthcare professionals responsible. The (optional) blood test will also be submitted as part of the participant's patient record in case further investigations are indicated.

To protect the confidentiality, all data leaving the NHS for analysis by the research team in the University of Nottingham will be de-identified. Participants will be assigned a study ID number which is different from NHS identifiers and does not include any personal identifiers for the participant. Participant identifiable data will be stripped from MRI scans and blood test results. REDCap software[38] will be used for the study electronic case report form (eCRF). De-

identified study data will be added to the study eCRF using the participant study ID. Therefore, patient identifiable data will not leave the NHS.

Adverse events

All adverse events will be recorded, assessed and closely monitored until resolution, stabilisation, or until it has been shown that the study intervention is not the cause. The Chief Investigator shall be informed immediately of any serious adverse events and shall determine seriousness and causality in conjunction with any treating medical practitioners. All intervention-related serious adverse events will be recorded and reported to the Research Ethics Committee as part of the annual reports. The Chief Investigator shall be responsible for all adverse event reporting.

Dissemination policy

The findings of the study will be communicated to the scientific community via one major peer-reviewed publication and several anticipated secondary peer reviewed publications, related to clinical genetics, paediatric oncology, health psychology or radiography / medical imaging. The results will also be presented at specialist meetings such as the A-T Clinical Research Conference meeting, and other relevant scientific meetings in fields such as clinical genetics and medical imaging.

Study approvals and status

The study was prospectively registered with ClinicalTrials.gov (NCT05252819) on 23rd February 2022. The study received a favourable Research Ethics Committee opinion from the United Kingdom NHS Health Research Authority (ref. 22/YH/0053) on 6th May 2022, and a minor amendment was approved on 20th April 2023. The current approved study protocol is version 2 dated 3rd April 2023. Recruitment commenced on 1st September 2022 and will close on 30th September 2023.

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Discussion

This will be the first feasibility study assessing the use of WBMRI for cancer surveillance in children and young people with A-T and evaluating the psychosocial impact of participating in a cancer surveillance programme.

A-T is a progressive disease that manifests in early childhood, with cancer being one of the most frequent reasons for mortality[4,7,39,40]. Despite the high cancer risk that people with A-T experience, cancer surveillance guidelines for management of children and young people with A-T are lacking [4,6,8,9,41].

The World Health Organization states that “early cancer diagnosis improves cancer outcomes by providing care at the earliest possible stage”[42]. Furthermore, detecting cancer in a late stage will affect not only the chances of treatment success (and consequently the problems associated with treatment), but it will also increase the costs of care [42]. Introduction of an imaging-based cancer surveillance programme – which this proposal is the first step towards - could benefit the children and families through earlier detection of treatable cancers. Importantly, detecting cancer in its early stage may allow less aggressive treatment with tailored radiation doses[1,3,9]. Indeed, it has been shown that dose-adapted therapy in people with A-T can significantly increase overall survival[9].

If this study proves the feasibility of this approach, we will aim to proceed to a large international trial to establish the efficacy and cost-effectiveness of this approach. This could have an important impact on clinical practice and patient care, as it could lead to development of cancer surveillance guidelines for people with A-T.

List of abbreviations

AACR - American Association for Cancer Research

CPS - cancer predisposition syndromes

A-T – Ataxia telangiectasia

ATM – Ataxia telangiectasia mutated

DWI – Diffusion-weighted imaging

MPRAGE – Magnetization-prepped rapid gradient echo

MRI – Magnetic resonance imaging

NHS – National Health Service

STIR – Short tau inversion recovery

WBMRI – Whole body magnetic resonance imaging

Declarations

i. Ethics approval and consent to participate

This study received a favourable Research Ethics Committee opinion from the United Kingdom National Health Service (NHS) Health Research Authority (ref. 22/YH/0053) on 6th May 2022. Amendments to the protocol approved by the Research Ethics Committee will be communicated directly with the Sponsor and Investigators. The study is sponsored by University of Nottingham Research and Innovation (Contact address: Jubilee Conference Centre, Triumph Road, Nottingham, NG8 1DH, United Kingdom). The sponsor has no role in the collection, analysis or presentation of data arising from the study.

Written informed consent will be obtained from participants aged 16 and over, or from the parent / guardian consent for participants aged 4 to 15 years. Additionally children and young people under age 16 years will be asked for their assent agreeing to participation.

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ii. Consent for publication (include appropriate statements)

Not applicable

iii. Availability of data and materials

All study documents can be shared on reasonable request to the corresponding author. In view of the small sample size for this feasibility study, and the rarity of childhood A-T, we will not be sharing individual participant data arising from the study in view of the risk of participant's being identified. This is consistent with the Research Ethics Committee approval for the study.

iv. Competing interests

None

v. Funding

This study is funded by a grant from Action for A-T (ref. 20NOT05). Renata Neves is supported by a Doctoral Fellowship awarded by the College of Radiographers (ref. DF021). The funders have no role in the collection, analysis or presentation of data arising from the study.

vi. Authors' contributions

RN and RAD performed the literature review, secured funding for the study, designed the study and drafted the manuscript. KC helped to draft the manuscript. RP, SW, MS, WPW, SJ, MD and CG secured funding for the study, supported the design of the trial. All authors edited the draft manuscript and approve the final manuscript.

vii. Acknowledgements

Not applicable

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