Growth and nutrition in children with ataxia telangiectasia

Emma Stewart, Andrew P Prayle, Alison Tooke, Sara Pasalodos, Mohnish Suri, Andy Bush, Jayesh M Bhatt

ABSTRACT

Background Ataxia telangiectasia (A-T) is a rare multisystem disease with high early mortality from lung disease and cancer. Nutritional failure adversely affects outcomes in many respiratory diseases. Several factors influence nutrition in children with A-T. We hypothesised that children with A-T have progressive growth failure and that early gastrostomy tube feeding (percutaneous endoscopic gastrostomy, PEG) is a favourable management option with good nutritional outcomes.

Methods Data were collected prospectively on weight, height and body mass index (BMI) at the national paediatric A-T clinic. Adequacy and safety of oral intake was assessed. Nutritional advice was given at each multidisciplinary review.

Results 101 children (51 girls) had 222 measurements (32 once, 32 twice, 24 thrice) between 2009 and 2016. Median (IQR) age was 9.3 (6.4 to 13.1) years. Mean (SD) weight, height and BMI Z-scores were respectively −1 (1.6), −1.2 (1.2) and −0.4 (1.4). 35/101 children had weight Z-scores below −2 on at least one occasion. Weight, height and BMI Z-scores declined over time. Decline was most obvious after 8 years of age. 14/101 (14%) children had a PEG, with longitudinal data available for 12. In a nested case control study, there was a trend for improvement in weight in those with a PEG (p=0.10).

Conclusions Patients with A-T decline in growth over time. There is an urgent need for new strategies, including an understanding of why growth falts. We suggest early proactive consideration of PEG from age 8 years onwards to prevent progressive growth failure.

BACKGROUND

Ataxia telangiectasia (A-T) is a rare autosomal recessive disease, caused by mutations in the ataxia telangiectasia-mutated (ATM) gene. This gene encodes a protein kinase, ATM, which is responsible for the cellular response to double-stranded DNA breaks. A-T causes progressive ataxia, immunodeficiency, sinopulmonary infections, oculocutaneous telangiectasia, increased cancer risk and increased sensitivity to therapeutic doses of ionising radiation. The most reliable estimates for the number of people with A-T, in the UK at least, are 3 per million and, it is estimated that 150 families are affected, with approximately 170 cases of A-T in the UK and Ireland (Professor AMR Taylor, School of Cancer Sciences, University of Birmingham, UK; personal communication). The median survival is 25 years, the leading causes of premature death being respiratory diseases and cancer.

What is already known on this topic?

- Small cross-sectional studies have shown that children with ataxia telangiectasia (A-T) have poor nutritional status.
- Patients with A-T die prematurely, the leading causes of death being respiratory diseases and cancer.
- Growth failure adversely impacts outcomes in many respiratory diseases.

What this study adds?

- Progressive growth failure becomes apparent in nearly a quarter of the children with A-T around 8 years of age.
- Seventy per cent of these children improved their weight Z-score after institution of gastrostomy feeding.

Undernutrition adversely affects lung health. Poor nutritional status and decreased pulmonary function have been shown to be linked in other diseases, including cystic fibrosis (CF). Worsening nutritional status increases infection-related morbidity and mortality. Malnutrition is of particular concern in children since it adversely affects normal accrual of height and weight and may impact lung development.

Small cross-sectional studies have shown that patients with A-T exhibit high rates of malnutrition, short stature and reduced lean body mass. Numerous factors including neurodegeneration, limited food intake with progressive disease, dysphagia and/or swallowing incoordination, limited physical activity, hormonal changes, hypogonadism, insulin resistance, glucose intolerance, abnormal expression of insulin-like growth factor (IGF) 1 (somatomedin C), low levels of insulin-like growth factor-binding protein 3 (IGFBP3), and infections and an associated hypercatabolic state all potentially contribute to poor growth. A-T causes extreme insulin resistance, but clinical diabetes is diagnosed infrequently and it is unclear whether the presence of diabetes also affects nutritional status and lung disease. Oropharyngeal dysphagia with aspiration is common and is progressive in older patients (second decade) with A-T. The onset of dysphagia coincides with a
decrease in nutritional status, although in a cross-sectional study it is not possible to distinguish between nutritional deficiency as a cause or effect of dysphagia. Hence, it is important to maintain good nutrition in children with A-T to protect respiratory function and to ensure normal growth.

We hypothesised that children with A-T have progressive growth failure and that early percutaneous endoscopic gastrostomy (PEG) feeding improves nutritional outcomes. We aimed longitudinally to assess the growth of children with A-T and to examine the effect of PEG insertion on their growth.

**METHODS**

Between May 2009 and April 2016, 101 children (51 girls) attended the national paediatric A-T clinic in Nottingham. Each child participated in multidisciplinary consultations, including a dietician, speech and language therapist, occupational therapist, neuromuscular and respiratory physiotherapist, respiratory paediatrician, neurologist, immunologist, geneticist and clinical psychologist. All children were diagnosed with A-T based on the WHO criteria. They are recalled for review at the clinic every 2 years or earlier if there are clinical concerns. The clinic records the age, height, weight and body mass index (BMI) of each child at every visit. Additional measurements were available in some children from their local clinics. It is also noted whether the child has a PEG in situ or has been referred for PEG insertion. The indications for PEG insertion were not protocol driven at the time of this analysis, but was a clinical decision taken individually for each patient after discussion with parents, either at the national clinic or at the local hospital by the local team, or both. Ethical approval was not required for this study as anthropometric data were recorded as per standard paediatric clinical care and any management advice was based on the clinical evaluation at the time of the assessment.

These data were collected prospectively in clinic by the respiratory paediatrician. In addition, retrospective data were taken from dieticians’ letters from each clinic. This included the dietician’s recommendations for continuing support as required. The dieticians used a four-tiered system of nutritional advice. The first level was standard nutritional advice. Second was fortification of food, for example, with full-fat milk and butter. Nutritional supplements were then recommended if the child’s growth continued to falter. Finally, PEG feeding would be advised if there is ongoing growth failure despite appropriate caloric intake and fortification. This was occasionally preceded by a short trial period of nasogastric tube feeding. Z-scores (SD scores) were then calculated for BMI, height for age and weight for age, using the WHO criteria. Z-scores below −2 mean the child is wasted, stunted or underweight, and below −3 severely wasted, stunted or underweight.

**Statistics**

The study reports on all patients seen at the National Children’s Ataxia Telangiectasia Clinic; therefore, a power calculation was inappropriate. We investigated the effect of age and presence of a PEG on weight Z-score. Using all the measurements per patient, a growth curve analysis of all patients was undertaken, comparing models with and without a fixed effect of age on Z-score.

Patients who had a PEG inserted were matched with control(s) by age and weight Z-score. We took the first weight measurement for each child with a PEG (or, for children with only one measurement with a PEG, the measurement immediately prior to this), and subtracted this from the final measurement in our dataset to give a change in weight over time for each patient with a PEG. We matched each of these cases with at least one control. Controls had age at baseline of <1 year away from the case, and were within one unit of Z-score from the case at baseline. We compared the trajectory of weight gain/loss over time with a sign test.

Data were analysed with R (R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. [Internet]. Available from: http://www.R-project.org) (V3.2.1 using the lme4 (Bates D, Mächler M, Bolker B, et al. Fitting linear mixed-effects models using lme4. J Stat Softw [Internet]. 2015 (cited 17 December 2015);67(1). Available from: http://www.jstatsoft.org/v67/i01/) package to fit the growth curve models). Full methods including illustrative code are available from the authors on request.

**RESULTS**

Of the 101 children who attended the clinic, 32 children had one set of measurements, 32 had two, 24 had three, 11 had four and 2 had five. Weight was recorded in all patients at every visit, a total of 222 measurements. Height and BMI were recorded 216 times (97%). The median and range of age, Z-scores for weight, height and BMI and the number of measurements that were underweight, stunted or wasted can be seen in table 1, which shows a significant proportion had Z-scores below −2. In total, 35/101 patients were underweight (Z-score weight less than −2) and 73/101 were stunted (height Z-score less than −2) on at least one occasion.

The trajectory of Z-scores for patients is shown in figure 1, with separate plots for weight, height and BMI. On inspection, the relationship appeared non-linear over time with a possible increase in the rate of decline in mid-childhood. A growth curve model was fitted to model weight Z-scores, using a random intercept for slope and intercept, with a linear fixed effect for age. The rate of decline of weight Z-score was 0.1 units per year (95% CI −0.2 to 0; analysis of variance comparing models with and without the fixed effect: p<0.01). This indicates that compared with a healthy population weight decreased year on year by 0.1 SDs (ie, the weight was low, and became increasingly lower).

| Table 1 | Median age, Z-scores for weight, height and body mass index (BMI) and the number of measurements that were underweight, stunted or wasted |
|------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| All visits             | Baseline N=32                                                                                                                  |
| Age in years (median and IQR) | 9.3 (6.4 to 13.1)                                                                         |
| Z-scores weight (mean Z-score and SD) | -1 (1.6)                                                                         |
| Height (mean Z-score and SD) | -1.2 (1.2)                                                                         |
| BMI (mean Z-score and SD) | -0.4 (1.4)                                                                         |
| Second visit N=32                                               | 10.0 (6.8 to 13.2)                                                                         |
| Z-scores weight (mean Z-score and SD) | -1 (1.5)                                                                         |
| Height (mean Z-score and SD) | -1.2 (1.1)                                                                         |
| BMI (mean Z-score and SD) | -0.3 (1.4)                                                                         |
| Third visit N=24                                               | 12.3 (6.4 to 15.5)                                                                         |
| Z-scores ≤−2 N (% of total measurements) | 59 (27%)                                                                         |
| N=28                                                                  | 47 (22%)                                                                         |
| N=24                                                                  | 28 (13%)                                                                         |
Longitudinal data were available for 25 underweight children. Of these, 10 had a PEG inserted, and of these 10, 7 improved their weight Z-score (figure 1B). Overall, of the 12 children for whom we have serial measurements of weight and a PEG was inserted, 9/12 improved their Z-score, for two there is currently only one measurement post PEG insertion (thus limited follow-up), and only one patient with a PEG declined in PEG weight Z-score on serial measurement post PEG insertion.

Twelve children with a PEG had multiple measurements, and we matched these children with 25 cases. Cases and controls are compared in table 2. The mean change in weight Z-score after insertion of a PEG during follow-up was 0.218 (SD 1.4), whereas for controls this was -0.4 (SD 0.9); Wilcoxon test p=0.06. Eight of 12 patients in the cases (67%) increased in weight, compared with 8/25 (32%) of controls (proportion test p=0.10).

**DISCUSSION**

We showed that there is a clinically important and statistically significant decline in weight and height Z-scores over time. Despite regular dietician advice, fortification of food and prescription of nutritional supplements, we have found that approximately a quarter of our clinic patients were defined as underweight and/or stunted at some point during the study period (Z-scores < -2).

The plots of individual trends in weight, height and BMI suggested that PEG insertion was associated with an improvement in weight Z-score. We used a nested case control study, matching at least two controls for every case in which a PEG was inserted, and for whom we had multiple measurements of weight. We took the first weight after PEG insertion (or the weight immediately prior to this if we only had one weight after PEG insertion) and found that patients with a PEG had on average weight gain, whereas controls without a PEG tended to lose weight. When comparing our data for weight Z-scores with each visit (table 1), we found that between visit 1 (median age 8.3 years) and visit 3 (median age 12.3) there is an obvious drop in Z-scores. We suspect that the drop in weight Z-score appears to commence at around the eighth birthday.

Nutritional failure and poor growth are well recognised in A-T. Voss et al found that 25% (N=6) patients whose height was below the third percentile were in the age group of 2–9 years. In this younger age group, the patients with A-T showed significantly lower levels of IGF-1 compared with healthy controls which was not seen in the older age group. IGFBP3 levels
in patients with A-T were also lower compared with the controls in both age groups. They concluded that patients with A-T exhibit growth retardation as well as growth hormone/IGF-1 deficiency. In a small Australian study which assessed nutritional status by measuring body cell mass (BCM), three out of four children who had height Z-scores of −2 or less were <9 years of age. Elhelayel et al. studied 13 patients with A-T (age 7.7 ±3.5 years, range: 3–14.5 years) and found height standard deviation score (SDS) of −1.4±1.2 with 38% of them having a score <−2. Thirty-one per cent of the patients had low BMI and 38% had low IGF-1. Thus, stunting in A-T appears to start in early childhood.

The high number of underweight and stunted children in comparison with those with low BMI highlights one of the disadvantages of using BMI as a nutritional measure. Those who are both short and thin may have a BMI within the normal range. A recent study using BCM found a much higher incidence of malnutrition (69%) that included children who were considered overweight by traditional measures. This may be reflected in the high proportion (47%–48%) of children in this study that decreased their BMI centile over time.

The proportion of PEGs (13.9%) in our cohort is identical to other large published series (14.6%). Early PEG placement in A-T and other neurological conditions is beneficial in terms of safety and caregiver satisfaction. Late placement is associated with poor outcomes, which is thought to be due to factors including advanced lung disease and malnutrition. Given the rarity of A-T, extrapolation from other conditions is inevitable. In children with CF, clinical audit and a structured nutritional intervention approach (with early referral for PEG in those with severe malnutrition), improved outcomes in terms of growth parameters, lung function and the 2-year survival post PEG insertion improved from 70% to 100%. The long-term nutritional benefit of PEG tube placement is critically dependent on presurgical pulmonary function with better growth if PEGs are placed early when the child has better pulmonary function.

A key strength of our study is the size in comparison with other A-T cohorts; we reported all 101 patients seen, and a total of 222 measurements, thus removing sampling bias. We are therefore able to provide relatively robust estimates of the rate of decline over the whole cohort. However, even though this is a large study in the field of A-T, overall the numbers are low, and so we have limited statistical power.

A clear limitation of our study is that patients received PEGs driven by perceived clinical need; this was neither protocised nor part of a randomised controlled trial (RCT). Clinical need is shown by the baseline weight Z-score in our cases (mean −2.4) versus controls (−1.2). An observational study such as this can only be hypothesis generating, and the findings of apparent benefit require prospective testing. Moreover, given our limited numbers, we cannot say for certain that a PEG is definitely associated with an increased rate of growth in those patients where one was inserted, though we have limited support for this from our nested case–control study. As PEG insertion is a rare intervention in an extremely rare disorder, we believe that finding robust evidence (eg, randomised clinical trial data) for its efficacy in A-T would be extremely challenging, and a RCT is unlikely to ever be performed due to clear feasibility difficulties. However, as many of our patient’s weight Z-scores improve with insertion of a PEG, this suggests that growth failure is not an inevitable consequence of A-T, but a complication that may be successfully managed with early intervention. It would be useful to know about the interactions between pulmonary function (often not measured because of coordination difficulties) and nutrition. Whether early PEG improves lung function and mortality in A-T is an important question for future studies.

This study is also limited by a lack of data on the precise (ie, day to day) nutritional intake and overall health of the children. Investigation of these aspects may provide insight into the reasons why these children have progressive growth failure. Other studies suggest that tiredness, taste fatigue, avoidance of foods that are difficult to swallow and poor appetite during respiratory infections all contribute to malnutrition. Our study is restricted in scope to studying the key features of the growth trajectories of children with A-T in our clinic. There are several areas that are ripe for future study, including the impact of puberty and sex hormones, and the impact of oromotor swallowing difficulties on nutrition. The absence of a pubertal assessment in particular is an acknowledged weakness of the study. We plan to report on these in future papers.

These clinical data confirm that there is progressive growth failure with increasing age in children with A-T. Particular attention to the nutrition of those over 8 years is essential, as this is when growth failure becomes apparent in the majority of children. Previous studies in A-T have shown that PEG insertion has very high levels of caregiver satisfaction and late PEG insertion is associated with adverse outcomes. We hypothesise that early intervention with PEG feeding for malnourished children is beneficial, ideally prior to significant growth failure, and our data are supportive of this. Given the low patient numbers, an RCT will not likely be possible. However, we will continue to
collect data within this national clinic, and we propose to care-
fully follow children to assess the efficacy of early PEG insertion
(prior to significant growth failure) and other early nutritional
interventions in A-T.

Acknowledgements AB was supported by the NIHR Respiratory Disease
Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation
Trust and Imperial College London. APP was supported by a NIHR ACL.

Contributors JMB, ES, APP, AT, SP and AB made substantial contributions to the
conceptualization of the work, or the acquisition, analysis or interpretation of
data. ES, APP, MS, SP, AB and JMB: drafting the work or revising it critically for
important intellectual content. JMB and AB: final approval of the version published.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES
1 Gatti RA. Ataxia Telangiectasia. In: GeneReviews. (cited 14 March 2015). http://
www.ncbi.nlm.nih.gov/books/NBK26468/
2 Woods CG, Bundey SE, Taylor AM. Unusual features in the inheritance of ataxia
telangiectasia. Hum Genet 1990;84:555–62.
3 Crawford TO. Survival probability in ataxia telangiectasia. Arch Dis Child
2005;91:610–1.
4 Bhatt JM, Bush A, van Gerven M, et al. ERS statement on the multidisciplinary
respiratory management of ataxia telangiectasia. Eur Respir Rev 2015;24:565–81.
5 Corey M, McLaughlin FJ, Williams M, et al. A comparison of survival, growth, and
pulmonary function in patients with cystic fibrosis in Boston and Toronto. J Clin
Epidemiol 1988;41:583–91.
6 Sharma R, Florea VG, Bolger AP, et al. Wasting as an independent predictor of
mortality in patients with cystic fibrosis. Thorax 2001;56:746–50.
7 Bresnahan KA, Tanumihardjo SA. Undernutrition, the acute phase response to
infection, and its effects on micronutrient status indicators. Adv Nutr
2014;5:702–11.
8 Girardet JP, Viola S. Nutrition and severe chronic respiratory diseases:
pathophysiological mechanisms. Pediatr Pulmonol 2001(Suppl 23):20–1.
9 Voss S, Pietzner J, Hoche F, et al. Growth retardation and growth hormone
deficiency in patients with Ataxia telangiectasia. Growth Factors 2014;32:123–9.
10 Schubert R, Reichenbach J, Zielen S. Growth factor deficiency in patients with ataxia
telangiectasia. Clin Exp Immunol 2005;140:517–19.
11 da Silva R, dos Santos-Valente EC, Burim Scomparini F, et al. The relationship
between nutritional status, vitamin A and zinc levels and oxidative stress in patients
with ataxia-telangiectasia. Allergol Immunopathol (Madr) 2014;42:329–35.
12 Ross LJ, Capra S, Baguley B, et al. Nutritional status of patients with ataxia-telangiectasia:
a case for early and ongoing nutrition support and intervention. J Paediatr Child Health
2015;51:802–7.
13 Peretz S, Jensen R, Baserga R, et al. ATM-dependent expression of the insulin-like
growth factor-I receptor in a pathway regulating radiation response. Proc Natl Acad
Sci USA 2001;98:1676–81.
14 Bar RS, Levis WR, Richter MM, et al. Extreme insulin resistance in ataxia telangiectasia:
defect in affinity of insulin receptors. N Engl J Med 1978;298:1164–71.
15 Schalch DS, McFarlin DE, Barlow MH. An unusual form of diabetes mellitus in
ataxia telangiectasia. N Engl J Med 1970;282:1396–402.
16 Morrell D, Chase CL, Kupper LL, et al. Diabetes mellitus in ataxia-telangiectasia,
Fanconi anemia, xeroderma pigmentosum, common variable immune deficiency,
and severe combined immune deficiency families. Diabetes 1986;35:143–7.
17 Robinson S, Kessling A. Diabetes secondary to genetic disorders. Baillière Clin
Endocrinol Metab 1992;6:867–98.
18 Lefton-Greif MA, Crawford TO, Winkelstein JA, et al. Oropharyngeal dysphagia and
aspiration in patients with ataxia-telangiectasia. J Pediatr 2000;136:225–31.
19 Notarangelo LD, Casanova JL, Fischer A, et al. Primary immunodeficiency diseases:
an update. J Allergy Clin Immunol 2004;114:677–87.
20 Global Database on Child Growth and Malnutrition. http://www.who.int/
nutgrowthdb/about/introduction/en/index4.html
21 Training Course on Child Growth Assessment, “Interpreting Growth Indicators”.
2008. http://www.who.int/childgrowth/training/module_c_interpreting_indicators.
pdf?ua=1
22 Eliayel M, Soliman A, De Sanctis V. Linear growth and endocrine function in
children with ataxia telangiectasia. Indian J Endocrinol Metab 2014;18(Suppl 1):
593–6.
23 Sharon A, McGrath-Morrow. Pulmonary function in children and young adults with
ataxia telangiectasia: PFTs in Children and Young Adults with A-T. Pediatr Pulmonol
2014;49:84–90.
24 Lefton-Greif MA, Crawford TO, McGrath-Morrow S, et al. Safety and caregiver
satisfaction with gastrostomy in patients with Ataxia Telangiectasia. Orphanet
J Rare Dis 2011;6:23.
25 Sy K, Mahant S, Taback N, et al. Enterostomy tube placement in children with spinal
muscular atrophy type 1. J Pediatr 2006;149:837–9.
26 Mahant S, Friedman JN, Connolly B, et al. Tube feeding and quality of life in
children with severe neurological impairment. Arch Dis Child 2009;94:668–73.
27 Leder O, Oliver MR, Heine RG, et al. Clinical audit results in earlier nutritional
intervention in malnourished children with cystic fibrosis with improved outcome.
J Paediatr Child Health 2015;51:988–93.
28 Ramirez R, Flibrun A, Hasan A, et al. Improving nutritional status in a pediatric cystic
fibrosis center. Pediatr Pulmonol 2015;50:544–51.
29 Walker SA, Gozal D. Pulmonary function correlates in the prediction of long-term
weight gain in cystic fibrosis patients with gastrostomy tube feedings. J Pediatr
Gastroenterol Nutr 1998;27:53–6.