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Title Page:

Title: Growth and Nutrition in Children with Ataxia Telangiectasia

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Abstract

Background: Ataxia Telangiectasia (A-T) is a rare multisystem disease with high early mortality from lung disease and cancer. Nutritional failure adversely impacts 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, or 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 (range) age was 9.3 (1.5 to 18.4) years. Mean (sd) weight, height and BMI Z-scores were respectively -1.03(1.57), -1.17 (1.18) and -0.36 (1.43). 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 (13.9%) 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 ($p = 0.06$).

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

What is known about this topic:

Small cross sectional studies have shown that children with 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 Ataxia Telangiectasia around 8 years of age.

70% of these children improved their weight Z-score after institution of gastrostomy feeding.

Background

Ataxia Telangiectasia (A-T) is a rare autosomal recessive disease, caused by mutations in the ATM (Ataxia-Telangiectasia mutated) gene. This gene encodes a protein kinase, ATM, which is responsible for the cellular response to double stranded DNA breaks (1). A-T causes progressive ataxia, immunodeficiency, sinopulmonary infections, oculocutaneous telangiectasia, increased cancer risk and increased sensitivity to therapeutic doses of ionising radiation (1). The most reliable estimates for the number of people with A-T, in the UK at least, are 3 per million (2) 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 (3) ;, the leading causes of premature death being respiratory diseases and cancer (4).

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) (5,6). Worsening nutritional status increases infection-related morbidity and mortality (7). Malnutrition is of particular concern in children since it adversely affects not only normal accrual of height and weight but may also impact lung development (8).

Small cross-sectional studies have shown that patients with A-T exhibit high rates of malnutrition, short stature and reduced lean body mass (9–12). 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 IGF1 (somatomedin C), low levels of IGFBP3 (insulin-like growth factor binding protein-3), and infections and an associated hyper-catabolic state all potentially contribute to poor growth (9,13). A-T causes extreme insulin resistance (14), but clinical diabetes is diagnosed infrequently (15–17) 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 (18). 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 feeding (PEG) 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 (19). They are recalled for review at the clinic every two 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 dieticians' 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

(standard deviation scores) were then calculated for BMI, height-for-age and weight-for-age, using WHO criteria (20). Z-scores below -2.0 mean the child is wasted, stunted or underweight (21), below -3.0 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 upon 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 upon 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 less than 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 (22) (version 3.2.1 using the **lme4** (23) package to fit the growth curve models). Full methods including illustrative code are available from the authors on request.

Results

Of the 101 children that attended the clinic, 32 children had one set of measurements, 32 had two, 24 had three, 11 had four and two 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% confidence interval: -0.15 to -0.04; ANOVA comparing models with and without the fixed effect: p = <0.01). This indicates that compared, to a healthy population, weight decreased year on year by 0.1 standard deviations (i.e. the weight was low, and became increasingly lower).

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 0.175 (sd 1.37), whereas for controls this was -0.384 (sd 0.93); sign test p = 0.06.

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 1/4 of our clinic patients were defined as underweight and/or stunted at some point during the study period (Z-scores less than -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 8th birthday.

Nutritional failure and poor growth are well recognised in A-T. Voss et al (9) found that 25% (N=6) patients whose height was below the ~~below the~~ 3rd percentile were in the 2 to 9-year-old age group. In this younger age group, the A-T patients showed significantly lower levels of

Insulin-like growth factor-1 IGF-1 compared with healthy controls which was not seen in the older age group. IGF-BP3 levels in A-T patients were also lower compared with the controls in both age groups. They concluded that A-T patients exhibit growth retardation as well as GH/IGF-1 deficiency. In a small Australian study which assessed nutritional status by measuring body cell mass (BCM) (12), 3 out of 4 children who had height Z-scores of -2 or less, were less than 9 years of age. Ehlayel et al (24) studied 13 patients with A-T (age 7.7 ± 3.5 years , range: 3–14.5 years) and found height SDS of −1.4 ± 1.2 with 38% of them having a score < −2. 31% 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 to 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 another large published series (14.6%) (25). Early PEG placement in A-T (26) and other neurological conditions (27,28) is beneficial in terms of safety and caregiver satisfaction. Late placement is associated with poor outcomes, thought to be due to factors including advanced lung disease and malnutrition (26). Given the rarity of A-T, extrapolation from other conditions is inevitable. In children with CF, clinical audit (29) and a structured nutritional intervention approach (30) (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 pre-

surgical pulmonary function with better growth if PEGs are placed early when the child has better pulmonary function (31).

A key strength of our study is the size in comparison to 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 protocolised nor part of a randomised controlled trial. Clinical need is shown by the baseline weight Z-score in our cases (mean –2.42) versus controls (-1.21). 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 (e.g. 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 patients 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 (i.e. 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 tiredness, taste fatigue, avoidance of foods that are difficult to swallow and poor appetite during respiratory infections all contribute to malnutrition (12,18). 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 upon 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, a randomised controlled trial will not likely be possible. However, we will continue to collect data within this national clinic, and we propose to carefully follow children to assess the efficacy of early PEG insertion (prior to significant growth failure) and other early nutritional interventions in A-T.

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Table 1: Median age, Z-scores for weight, height and BMI and the number of measurements that were underweight, stunted or wasted.

		All visits	Z-scores ≤ -2.0 = N (% of total measurements)	Baseline N = 32	Second visit N = 32	Third visit N = 32
Age in years (median and interquartile range)		9.326 (1.536.4 to 1813.1.38)		8.3 (1.54.3 to 11.318.38)	9.9710.0 (6.84.3 to 13.216.8)	12.31 (6.4 to 117.75.5)
Z-scores (mean and sd)	Weight	-1.0329 (1.657)	59 (276.6%)	-0.97 (1.61)	-0.95 (1.548)	-1.33 (1.52)
	Height	-1.217 (1.218)	47 (221.8%)	-1.16 (1.326)	-1.216 (1.14)	-1.326 (0.951.0)
	BMI	-0.357 4 (1.43)	28 (133.0%)	-0.31 (1.34)	-0.30 (1.354)	-0.78 8 (1.875)

Table 2: Comparison of cases and controls in nested case/control study.

	Cases	Controls
N	12	25
Number Female (%)	5 (42%)	17 (68%)
Age at baseline, Median [rangeIQR]	10.7 [8.2 to 13.47.9 to 14.7]	9.1 [8.4 to 10.47.6 to 15.2]
Duration of follow up, years Median [rangeIQR]	2.43 [2.0 to 3.6 0.4 to 6.1]	2.6 [1.3 to 4.30.4 to 5.68]
Baseline weight Z- score Mean (sd)	-2.42 (1.64)	-1.21 (1.091)
Change in Z-score for weight per year Median [IQR]	0.2 [-0.3 to 0.4]	-0.2 [-0.4 to 0.0]
Proportion (percent) of patients with increasing weight over time	8 / 12 (67%)	8 / 25 (32%)

Figure 1. Scatter plots showing the trajectories of weight (A and B), height (C) and BMI (D). Individual patients' trajectories are shown by joining points of measurement with a straight line. Only patients with multiple measurements are shown. If the patient did not have a PEG at the time of measurement, the point is a hollow circle, whereas the presence of a PEG is denoted with a filled black circle. Similarly lines are grey for patients who never had a PEG, but if a patient has ever had a PEG, then the line is black to allow identification of individual patients' trajectories. Panel B shows only individuals who had a PEG in situ, to allow an appreciation of the trajectories for these patients.