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Title: Nutritional status in adolescents with esophageal atresia

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ABSTRACT

Objectives: Growth may be compromised in children with esophageal atresia (EA), but among factors important for growth and development, nutrition is only barely studied. The aim of this study was to examine nutritional status in adolescents with EA.

Methods: Anthropometric measurements, blood samples, pH-measuring, mapping of dysphagia with a modified EAT-10 questionnaire, 4-day dietary record and a semi-structured interview about eating habits and nutrition counselling were applied.

Results: Out of 102 eligible adolescents with EA, 68 (67 %) participated in this cross-sectional study. Median height SDS was -0.6 (-4.6-1.8). Ten (15 %) were classified as stunted (height SDS < -2). Fourteen (21 %) were overweight. More than 2/3 reported symptoms of dysphagia (EAT-10 score ≥ 3) and avoided specific foods. Forty-eight (71 %) completed the 4-day dietary record, which showed daily intake of energy below age-appropriate recommendations. One-third reported an energy intake below estimated basal metabolic rate. Only 24% had counselled a dietitian.

Conclusion: EA-adolescents have growth below reference values and energy intake below recommendations. One-third of the adolescents reported intake below estimated basal metabolic rate. Even if the rate of underreporting may be high, energy intake and its relation to stunting needs to be further studied in EA patients.

Introduction

Esophageal atresia (EA) is a rare congenital malformation (1, 2), with major therapeutic challenges and consequences for feeding both in infancy and childhood (1, 3-5). Known underlying mechanisms for the feeding difficulties include dysphagia expressed through swallowing disorders and esophageal dysmotility, and gastroesophageal reflux disease (GERD) (6-9). Feeding difficulties in childhood, long-term dysphagia and gastrointestinal problems may have consequences for the nutritional status and growth potential later in life (3, 7, 8, 10). The growth of children with EA is reported to be below the reference norm during the first years of life (11, 12). Menzies et al. have presented prevalence of growth deficiencies in children with EA (median age 3.7 years) with wasting in 18% and stunting in 9% (12), whereas Vergouwe et al. showed that growth was below the reference norm during the first years of life, but had normalized at 12 years (11). There are few studies on growth into adolescence and adulthood. Dietary assessments in terms of intake of energy and micronutrients in EA patients are also lacking. The primary aim of the present study was to describe nutrition status including anthropometry, dietary intake and micronutrient status in adolescents with EA.

Method

Population

Between January 1996 and December 2002, 125 neonates with EA were admitted to a tertiary hospital in Norway for surgical repair (Figure 1). Of these, 109 were long term survivors and eligible for this cross-sectional study performed in 2015-2017. Seven patients were excluded. Exclusion criteria were additional conditions associated with growth disorders (cerebral palsy, muscular dystrophy, Down syndrome) or mental retardation leaving the EA adolescent unable to answer questionnaires. Non-Norwegian speakers were also excluded. All participants

signed an informed consent. The study was approved by the Regional Ethical Committee (REK) in Norway. Reference number: 2014/1224.

Clinical characteristics

Medical records were reviewed for the type of EA according to Gross classification (13), neonatal data, associated anomalies, length of postnatal hospital stay and esophageal dilatations for stenosis. VACTERL syndrome was defined according to Solomon (14).

Follow-up visit

At the follow-up visit, nutritional status was evaluated by anthropometric measurements, biochemical parameters and nutritional intake. The examination also included a semi-structured interview regarding eating habits and nutrition counselling, pH-measuring and assessments of dysphagia and symptoms of gastroesophageal reflux disease (GERD).

Anthropometry

Participant's height (cm) and weight (kg) were measured by trained personnel using standardized measuring equipment. Sex- and age-adjusted standard deviation scores (SDS) were calculated for height (height-for-age (HFA)) and body mass index (BMI) by using the Norwegian national reference standards (15, 16) and a growth analyzer calculation tool (Vekstjournalen). According to the World Health Organization (WHO), stunting was defined as height SDS < -2. BMI SDS < -2.0 and > 1.0 were used as cut-off points to classify wasting and overweight (including obesity), respectively (17). Scoliosis was diagnosed by radiological assessment of Cobb's angle, and a Cobb angle over 40° was defined as severe scoliosis (18).

Biochemical parameters

Non-fasting blood samples were drawn for evaluation of nutritional status and factors associated with growth. Reference values were based on reference ranges from Oslo University Hospital, except for iron status where we used WHO's cut-off values. Iron deficiency was defined by serum ferritin < 15 micrograms/L (19). Vitamin D deficiency was considered to be present at P-25-OH-vitamin D total < 50 nmol/L, whereas severe vitamin D deficiency was defined by a threshold < 25 nmol/L according to European guidelines (20).

Nutritional intake

For dietary assessment, participants were instructed by a dietitian to register the intake of all food and beverages during a 4-day period, preferably 3 weekdays and 1 weekend day as recommended (21). Detailed information about dietary supplements was not mapped through the registration form. The dietary records were completed primary by the adolescents themselves, with help from parents when needed. They were asked to give detailed descriptions of the *type* of food and beverages, as well as the *amount* consumed. A validated booklet containing photographs of foods was used to estimate portion sizes (22, 23). Energy and micronutrient intakes were calculated using the software Kostholdsplanleggeren (24) which was based on Norwegian food composition tables (25). Energy- and micronutrient intake (vitamin A, D, C, thiamin, riboflavin, folate, calcium and iron) was compared to national recommendations (26). Micronutrient intake was also expressed as nutrient density of the diet (intake per unit of energy), and by comparison with average requirements (AR) (27).

Participants that completely failed to complete dietary records diaries were excluded from analysis of nutrient intake. To evaluate participants registered energy intake, we compared estimated intake with calculated individual basal metabolic rate (BMR). BMR is the amount

of energy needed for maintaining vital processes of the body not including activity and food processing. We used Schofield equation which allows us to estimate the basal metabolic rate (BMR) based on gender, age and weight (28).

Semi-structured interview regarding eating habits and nutrition counselling

Information about eating habits, use of dietary supplements and previous counselling by a dietitian was obtained by a questionnaire designed by the dietitian for this study.

Dysphagia

To identify dysphagia we used a questionnaire, slightly modified from the validated tool EAT-10. EAT-10 is a self-report dysphagia assessment tool where patients answer if, and to what extent, they experience swallowing difficulties (29, 30). The original EAT-10 consists of 10 questions, where each question is scored from 0 (no problem) to 4 (severe problem). A total score of “3” or higher is deemed to be abnormal (31). In the modified EAT-10 used in this study, seven of the questions were translated to Norwegian without any adjustments. The last three questions were slightly adapted for this specific patient group to obtain information regarding fluid intake during meals, time spent on meals and whether the adolescent tended to avoid eating together with friends because of his/her swallowing difficulties. The questionnaire was self-administrated and completed in less than 2 minutes.

pH-testing

The methods for esophageal pH testing followed standard procedures where all antacid medication was stopped 7 days prior to planned examination. After probe insertion to the ventricle, the probe was withdrawn with help of fluorescence until the tip was located above 2 vertebral bodies above the diaphragm. This placement was to make sure the probe was above

the diaphragm and above the potentially withdrawn z-line which may be case in some EA patients. The following day all patients were examined with upper endoscopy. Acid exposure to esophagus was considered normal with reflux- index (RI) $< 3\%$, intermediate between 3% - 7% , and abnormal $> 7\%$ (32)

GERD

Gastroesophageal reflux disease (GERD) was registered if the participants had troublesome reflux symptoms (regurgitation, vomiting, throat/retrosternal pain), if they used antacid medication on a regular basis, or if they previously had had anti-reflux surgery performed.

Statistical analysis

Data was extracted into an electronic spreadsheet and statistical analyses were performed using SPSS version 25.0. Results are presented as median (range, percentiles) or means with standard deviations (SD). Differences between two groups were analyzed using non parametric tests (Mann-Whitney U) and parametric tests (Student t-test). The Spearman's Rank Correlation Coefficient was used to discover the strength of a link between two sets of data. Statistical significance was accepted if the p-value was < 0.05 .

Results

Of the 102 adolescents invited for the study (Figure 1), 34 patients did not respond and 68 participated yielding a total response of 67%. There were 28 females and 40 males, and median age at follow-up was 16 (13-20) years; 50 in the age-group 14-17 years and 18 > 18 years. Of the total of 68 participants, 20 were excluded from analysis of nutrient intake because 14 did not return food diaries and 5 returned incomplete diaries (Figure 1).

There were no significant differences between attending and non-attending EA adolescents with respect to gender, gestational age, type of EA or associated anomalies (data not shown). Characteristics of the participants are presented in table 1. According to the Gross classification, EA type C occurred in 58 (85%), and among the remaining patients 3 (4.5%) were type A, 4 (6.0%) type D and 3 (4.5%) type E, respectively. Data about growth and dietary intake were analyzed in age groups according to growth references and recommended dietary intakes; ; 14-17 years and > 18 years respectively.

Anthropometry

Height SDS and BMI SDS at follow-up are shown in table 1. Ten adolescents (15%) were defined as stunted, including three with severe scoliosis. Exclusion of the participants with scoliosis did not change the median height SDS, respectively -0.6 (-3.3-1.8) without scoliosis and -0.6 (-4.6-1.8) in the total group. Adolescents with stunting had significantly lower birth weight ($p=0.015$), longer postnatal hospital stay ($p<0.001$), more esophageal dilatations before 12 months of age ($p<0.001$), more esophageal dilatations in total ($p=0.002$), a history of gastrostomy feeding ($p<0.001$) and more dysphagia based on results from EAT-10 ($p=0.026$). Height SDS in males was significantly higher in the youngest (14-17 years) compared to the oldest (>18 years), ($p=0.004$). In females there were no differences in height SDS between the age groups ($p=0.941$). Neither height nor weight were correlated to the presence of associated anomalies.

Only 2 (3%) adolescents were categorized as wasted (BMI SDS < -2), whereas 14 (21%), 7 females and 7 males, were overweight (BMI SDS > 1). The height SDS among the overweight adolescents was not different from the rest of the group.

Biochemical parameters

Median values for biochemical parameters are given in table 2. Most of the micronutrient parameters were within normal range except for vitamin D, folate and iron status. Thirty (44%) were diagnosed with vitamin D deficiency and three (4%) had severe vitamin D deficiency. We did not find any association between vitamin D deficiency and height SDS ($p=0.072$). According to WHO cut off values, seven (10%) of the participants had iron deficiency (ferritin < 15 micrograms/L), of which 18 % were females and 5 % were males. When evaluating all biochemical indicators of iron status (hemoglobin, ferritin, serum iron, transferrin, TIBC, transferrin saturation and transferrin-receptor), 15 % of the participants were considered to have insufficient iron status.

Nutritional intake

Data on nutritional intake from the 48 adolescents who completed the dietary records, is shown in table 3. None of the participants had a gastrostomy. Energy intake was 6.4 MJ (SD 1.5) /day in females 14-17 years, 8.3 MJ (SD 3.0)/day in females > 18 years, 9.7 MJ (SD 3.0) /day in males 14-17 years and 10.1 MJ (SD 3.0)/day in males > 18 years. Energy intake was lower than the age appropriate recommendations for females and males in both age-groups, and especially low for the youngest females (58% of recommended intake) (table 3). The energy intake in adolescents with cardiac malformations was not different from the rest of the group. There were no correlations between energy intake and weight SDS ($r=0.01$), height SDS ($r=0.20$), or BMI SDS ($r=0.20$). Median ratio energy intake/estimated BMR for all participants was 1.3 (0.8-2.4), and fifteen (31%) had an energy intake below their estimated BMR.

On average, macronutrients (proteins, fats and carbohydrates) contributed to total energy intake in the following way; 18 % from protein, 37% from fat and 46 % from carbohydrates. Diet composition of macronutrients was in accordance with recommendations (26) except for saturated fat and sugar. One adolescent (2 %) met the recommended intake of saturated fatty acids (< 10 % of total energy intake) and 29 (60 %) for sugar (< 10 % of total energy intake).

Nearly half of the adolescents (47 %) used dietary supplements, but no one reported to consume any kind of energy-containing supplements. Because of insufficient information about brand names and dosages, dietary supplements were not included when analyzing the participants' micronutrient intake.

Based on the 4-day dietary records median intake of all micronutrients was, except thiamin-, riboflavin- and calcium-intake in males, found to be below recommendations (table 3).

Intakes of micronutrients below average recommendations (AR) were most commonly seen for vitamin C, vitamin D and iron. Nutrient density (intake per unit of energy) was, compared to the recommendations (27), sufficient for most nutrients, but inadequate for iron, folate and vitamin D.

Nutrition counselling

Sixteen of the patients (24%) had received nutrition counselling from a dietitian, in early childhood. The proportion of adolescents with stunting was higher among those who had visited a dietitian ($p=0.003$), but otherwise there were no differences in any aspect of nutrition and health between those who had visited a dietitian and those who had not.

Eating habits

According to the semi-structured interview 48 (71 %) participants avoided specific foods. Twenty-four (50%) reported food texture as the reason for avoidance, and especially meat and meat-related products were reported to be challenging. Fourteen (21%) and 19 (28%) reported food dislikes as the reason for avoidance of fruits and vegetables respectively. Ten (15%) reported prolonged mealtime duration (more than 30 minutes) for dinner, but to a lesser extent for other meals.

Dysphagia and gastroesophageal reflux

Prevalence of self-reported swallowing difficulties and GERD are shown in table 1. Twenty-four females (86%) and 23 (59%) males had current swallowing difficulties according to the modified EAT-10 questionnaire. The most frequently reported challenges were: food getting stuck during swallowing (65%), need of extra liquids to manage swallowing (59%), difficulties with swallowing solid foods (56%) and pills (47%). None of the participants reported pain to be associated to swallowing. Swallowing difficulties expressed as total EAT-10 score was not significantly correlated with total energy intake ($p=0.81$), energy intake related to body weight (MJ/kg, $p=0.98$) or ratio energy intake/estimated BMR ($p=0.69$). Nine (13%) adolescents did not want to undergo pH-metry. 39 (66%) adolescents had normal RI, 13 (22%) had intermediate, and 7 (12%) had $RI > 7\%$. Fourteen (14/44, 32%) with symptoms corresponding to GERD (regurgitation, vomiting, throat and retrosternal pain) used medical antireflux therapy on a regular basis. We did not find any statistical correlation between pH-metry and nutrient intake (MJ/kg, $p=0.65$), nor between pH-metry and height SDS ($p=0.06$).

Discussion

To our knowledge, this is the first study on nutritional intake in adolescents with EA. We found that calculated energy intake was below age-appropriate recommendations, and below estimated basal metabolic rate in one-third of the participants. Estimated intake of micronutrients based on dietary records, not including dietary supplements, also reveal low intake especially for vitamin D and iron.

In the current study the adolescents' energy intake was lower than national recommendations. However, national recommendations are not the same as reference values on dietary intake. Comparing our results with data from dietary surveys, the intake in EA patients does not seem so discordant. In a Norwegian dietary survey 13 year old adolescents reported mean energy intake to be 7.4 MJ (SD 2.6)/day for females and 8.6 MJ (SD 2.7) /day for males (33), compared to mean values of 6.4 MJ (SD 1.5) and 9.7 MJ (SD 3.0) in our study. Another national study summarized mean energy intake in adults 18-29 years to be 8.1 MJ (SD 2.5) /day for females and 12.8 MJ (SD 4.0) /day for males (34), compared with mean intake of 8.3 MJ (SD 3.0) and 10.1 MJ (SD 3.0) for the oldest females and males in our study. This means that findings in our study are consistent with research showing adolescents' energy intake to be lower than national recommendations.

The low ratio energy intake/estimated BMR (median 1.3) found in our study indicates an energy intake not compatible with normal physical activity. Unfortunately physical activity was not registered in this study. According to Nordic nutrient recommendations 2012 a ratio of total energy expenditure/ estimated BMR < 1.66 refers to a low physical activity in adolescents 10-18 years (27). Thus, a possible explanation for the low ratio may be that EA adolescents are less active than healthy adolescents. Another possible explanation may be

underreporting of energy intake. Challenges in evaluation and validation of self-reported energy intake are well known (36, 37), and there is no reason to assume that adolescents with EA are different from other adolescents in respect of this.

Estimated intake of vitamin D and iron was below recommendations. However, these results may be uncertain because intakes of dietary supplements were not included. On the other hand, low vitamin D intake corresponds well with the blood analysis confirming deficient intake of vitamin D and iron. Further, low vitamin D intake corresponds with results from national dietary surveys (33, 34), and vitamin D deficiency has also been reported to be evident throughout the European population (35). Norwegian surveys are scarce, but a recent study from the northern part of Norway reported 60.2% of healthy adolescents (15-18 years old) to be vitamin D deficient (36). Iron deficiency in adolescents with EA also seems to be comparable with healthy, Norwegian adolescents. Handeland et al presented in a recent study that 9.7% of participants (n=478, mean age 14.6 years) had iron deficiency (ferritin < 15 µg/l (37). Thus, based on the fact that frequencies of deficiencies in vitamin D and iron were similar to those observed in the general population, it does not seem appropriate to attribute the observed deficiencies only to the disease under study. Notably, avoidance of fruits and vegetables caused by dislikes was reported in our study. This could be a factor that affect micronutrient intake, but we do not have sufficient detailed information to confirm this assumption.

Longitudinal data on growth in EA patients are few (10). A recent study demonstrated restricted growth in childhood, with height improvement in early adolescence (11), and Chetcuti & Phelan have reported normal height in adults with EA (38). On the other hand the rate of reduced growth in our study is in accordance with earlier reports (39, 40) with

Okuyaga et al also reporting adults with EA to be short (39). Height SDS was lower in the oldest males compared with the younger in our study. We do not find any obvious reasons to assume that the difference between age-groups are caused by changes in surgical or rehabilitations factors in recent years, but advances in neonatal medical care may have had an impact.

A majority of the adolescents in our study had swallowing difficulties and reported food textures as a factor influencing food choice. Previous studies have identified dysphagia and feeding behaviors as main causes of nutritional problems in patients with EA (1, 6, 12). We found a relation between stunting and dysphagia, but surprisingly there were no associations between self-reported dysphagia and nutrient intake. The reason for this discrepancy may be that the dysphagia have had influence on growth in childhood. During life the adolescence may have developed compensatory eating behaviors like limiting bolus size, slowing rate of eating and diet modification enabling the patient to normalize nutrient intake.

In this study we focused on nutritional intake, but there may of course be additional reasons for both dysphagia and impaired growth in EA patients. Among these comorbidities, esophageal dysmotility, gastroesophageal reflux disease and esophagitis are the most relevant in patients with esophageal atresia. Even though it is possible that stunting is caused by nutritional conditions in early childhood, other unidentified factors related to the primary diagnosis may also contribute to deviant development in children with esophageal atresia. In our rather small series of patients we found no significant relations to any of these conditions, but these are highly relevant to study in larger series of patients.

Despite challenges with growth, feeding and nutrient intake, only 24% of the participants had ever consulted a dietitian, which is in accordance with other studies in patients with esophageal atresia. In our study the prevalence of stunting was higher among participants who had visited a dietitian in childhood. The reason for this may be that there had been early concerns related to nutrition which had not been followed up. A recent study by Menzies et al, reported that 75% of EA patients were reviewed by a dietitian and/or speech therapist at their initial appointment after discharge, but long-term evaluation is lacking (12). The pubertal growth phase is considered an additional window of opportunity for nutritional intervention (41), which support a need for multidisciplinary follow up, including a dietitian, to prevent and treat feeding difficulties and nutritional challenges (7, 42, 43).

Strengths of the present study include the long-term perspective in adolescents with EA and the relatively high number of patients. However, information regarding growth development and nutrient intake from early childhood is lacking. Another disadvantage in this study is the lack of knowledge about parental height, and the participants' physical activity level in order to evaluate and validate their reported energy intake. The modified EAT-10 questionnaire developed for this study was unfortunately not validated for translation to Norwegian. The population in our study was heterogeneous from 13-20 years of age, including different types of malformations and different lasting comorbidities, but prevalence of different types of malformations and associated anomalies was comparable with previous studies on EA patients (40, 44). However, since less than 50% of the eligible population underwent the 4 day dietary records, the results need to be interpreted with caution.

The current recording of dietary intake is also limited by the lack of including micronutrients from dietary supplements. Furthermore, dietary records are regarded as the “gold standard” among dietary assessment methods, but there is a risk of under- and overreporting in all types

of diet surveys (45-47). Underreporting of energy intake may obviously be a great challenge in our study. According to Forrestal adolescents tend to underreport energy intake with the largest biases when using food records (48). Furthermore the dietitian did not do a quality control of the questionnaires which could have been a measure improving quality of the answers. Web-based dietary assessment methods might be preferred, but there is a need for more research and practical experience before such methods can be used routinely (49). Analysis of food intake only indicate a probability whether intake is in fact adequate or not. Nutrient intake data are not absolute values but are calculated using food composition tables and reported food consumption, both of which have a considerable error margin (27).

Conclusion, including implications and future perspectives

Patients with EA have lasting problems with dysphagia and growth below reference values. Based on dietary assessments we suspect an inadequate intake of energy in adolescents with esophageal atresia. Thus, the implications of this study are that patients with esophageal atresia should be followed into adolescence by a dietitian, and that growth and nutritional intake has to be recorded in larger studies.

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