Prospective long-term follow up of children with anorectal malformation: Growth and development until 5 years of age☆☆

Desiree van den Hondel, Cornelius E.J. Sloots, Saskia J. Gischler, Conny J.H.M. Meeussen, Rene M.H. Wijnen, Hanneke IJsselstijn*
On behalf of the Surgical Long-term Follow Up team

Department of Pediatric Surgery, Erasmus MC, Sophia Children's Hospital, 3000 CB, Rotterdam, the Netherlands

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Abstract
Background/purpose: To evaluate growth and development in children with anorectal malformations and to analyze effects of type of malformation and comorbidities.
Methods: Non-syndromal children with anorectal malformations were prospectively evaluated at 0.5, 1, 2, and 5 years. Biometrics were obtained at all visits. Mental and psychomotor function development was determined.
Results: 108 children (59% male) were included. 49% had a high malformation, and 46% had ≥1 additional major comorbidity. All growth parameters were below the norm at all ages (p<0.01), irrespective of type of malformation. Children with ≥1 additional major anomaly had lower height at all ages; at 5 years, mean (95% CI) height was −1.83 (−2.7 to −1.1) and −0.70 (−1.3 to −0.1) in children with and without comorbidities, respectively (p=0.019). Mental development was normal, irrespective of the type of malformation or comorbidities. Motor development was delayed at all ages. At 5 years, motor development (n=30) was normal in 70%, borderline in 23%, and 7% had definitive motor problems (p=0.043).
Conclusion: Non-syndromal children with anorectal malformations are at risk for growth impairment, especially those with additional major comorbidity. Mental development is normal. Motor development is slightly impaired. Supportive care should focus on growth, dietary management, and motor development besides defecation problems.

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We hypothesized that children with anorectal malformations are at risk for growth and developmental disorders, because of their additional comorbidity and their frequent hospital admissions in early life. Hence, in order to shed more light on this matter, we conducted this prospective follow up study as part of our structured follow up program for children with congenital anatomical malformations.
Anorectal malformations are congenital malformations varying from minor to very complex malformations. They occur in approximately 1 in 5000 live births. It is well-known that children with anorectal malformations have many surgical challenges, such as pelvic floor dysfunction [1], but little is known on the general health issues involved, such as growth and development. The only study on growth was a cross-sectional study in 34 children with anorectal malformations (mean age 11 years); these children showed a normal growth [2]. To date, long-term motor function development of children with anorectal malformations has not been studied or described. Three studies dealt with intelligence and educational performance [2–4]. One described a normal intelligence, the other two described learning problems and lower completed educational level.

Gischler and co-workers have shown that in newborns with severe anatomical malformations [5], factors such as number of associated anomalies, duration of hospital admission, and number of surgical interventions may negatively influence growth and development within the first two years of life [6]. Long-term multidisciplinary follow up is important in these children, aiming at monitoring growth and development, and providing, when indicated, early intervention.

We hypothesized that children with anorectal malformations are at risk for impaired growth and development at the long-term, notably those with serious comorbidity. To test this hypothesis, we prospectively evaluated physical growth and mental and motor development in children with anorectal malformations, treated in our hospital at various ages, until the age of 5. In addition, we analyzed possible effects of the type of malformation and the presence of comorbidity on the growth and development.

### 1. Patients and methods

All children with an anorectal malformation born between January 1999 and March 2011 who participated in our structured follow up program for congenital malformation survivors [6] were included in this study. This program aims to regularly assess growth, developmental parameters, and lung function when appropriate, until 18 years of age [6]. The assessment protocol is the standard of care at the Erasmus MC-Sophia Children’s Hospital. The Erasmus MC Medical Ethical Review Board (IRB) ruled that the “Medical Research in Human Subjects Act” does not apply to this research proposal, since subjects are not being submitted to any handling, nor are there rules of human behavior being imposed. Therefore, IRB approval was waived. All parents were informed about the study and provided permission to use the data for research purposes. Data were evaluated at the end of 2011. For the purpose of this study, we evaluated data at the ages of 0.5, 1, 2, and 5 years.

The following data were retrieved from the medical records: sex, gestational age, birth weight, type of malformation, number and type of associated anomalies, presence of a syndromal disorder, and number and type of surgical interventions. We classified the malformations as low and high, according to Rintala and co-workers [1]. Low malformations include anal stenosis, perineal fistula, and vestibular fistula. High malformations include rectourethral fistula, rectovesical fistula, anal atresia without fistula, rectum atresia, and persisting cloaca.

We classified the comorbidity as major or minor. Ravitch’s pediatric surgical index diagnoses [5] (e.g. esophageal atresia), cardiac malformations requiring operative correction or follow up by a pediatric cardiologist, other congenital malformations requiring major surgical interventions, or malformations seriously affecting normal function (e.g. tethered cord with neurogenic bladder function) were considered major. All other anomalies were considered minor (e.g. a small atrial septal defect closing spontaneously). Children with urologic problems were referred to a pediatric urologist to follow-up renal and bladder function. For patients with urologic comorbidity, serum creatinine levels were administered and compared with reference values [7,8]. Prematurity was defined as a gestational age of less than 37 weeks. Small for gestational age was defined as a birth weight for gestational age of $<−2$ SD from the Dutch reference values [9].

#### 1.1. Physical growth

Children with a syndromal or chromosomal disorder with known influence on physical growth were excluded for the evaluation of physical growth and development. Children with an unconfirmed but suspected syndromal diagnosis were excluded.

At each contact moment, we calculated the standard deviation scores (SDS) for height, weight for height, and head circumference (the latter until 2 years of age), and corrected for ethnicity [10–12]. The Dutch normative data have been collected cross-sectionally in a total of 14,500 children. For Dutch children of Turkish or Moroccan origin, normative data were collected in 2904 and 2880 children of Turkish and Moroccan origin, respectively, living in the largest four cities in the Netherlands. Further, we corrected for prematurity until 2 years of age [10]. Target height (TH) is structurally recorded since January 2011; in earlier years it was recorded on indication only [13]. The target height range (THR) was defined as TH in SDS $±1.3$. A persisting growth problem was defined as two contact moments with SDS height $<−2$ or below the THR, and lack of a normal growth at a later contact moment.

#### 1.2. Development

Within the framework of the follow up program, the Dutch translation of the Bayley Developmental Scales (BOS 2–30) had been administered until the age of 2 years. This
standardized instrument assesses both mental and motor development of 2 to 30-month-old children [14]. From December 2003 onwards, a new version of the BOS 2–30 was used: the Bailey Scales of Infant Development-Second Edition-Dutch version (BSID-II-NL) [15]. The BOS 2–30 and the BSID-II-NL share the same background and are substantially related to each other [16]. Both tests provide a mental developmental index (MDI) and a psychomotor developmental index (PDI) with a mean (SD) of the normative population of 100 (15). We clustered the results into normal (≥−1 SD), mild developmental delay (−2 to −1 SD), and severe developmental delay (≤−2 SD). We identified the children with a developmental delay (mild or severe) at any contact moment, and lack of a score in the normal range at a later contact moment, and clustered them as such.

At 5 years of age, both the short version of the Revised Amsterdam Intelligence Test (RAKIT) and the Movement Assessment Battery for Children (MABC) were administered, as described previously [17]. For the RAKIT [18], the mean (SD) score of the normative population is 100 (15). The MABC [19] presents a total impairment score (TIS) and three subtest scores: manual dexterity, ball skills, and balance skills. The MABC test results are expressed in percentiles, which we clustered into normal (>p15), borderline (p6-p15), and definite motor problem (≤p5). The maximal exercise capacity was tested with the Bruce treadmill protocol at 5 years of age. This yielded a maximal endurance time which was converted to SDS using recently published Dutch reference values [20].

1.3. Data analysis

The distribution of the numerical data was tested with the Shapiro–Wilk test. Numerical data are presented as mean scores and 95% confidence intervals (CI), or as median and range when appropriate. Categorical data are presented with numbers (n) and percentages. Numerical data were tested with the reference population with the one-sample t-test, means between groups were compared using the independent samples t-test. Proportions were compared to the normative population with the Chi-square test. Statistical analysis was performed using SPSS 17.0 for Windows, with the significance level set at p<0.05.

2. Results

In the study period, 152 children were treated for anorectal malformations in our hospital; treatment of 8 of them had been initiated elsewhere. Eleven children died at a young age due to severe comorbidity: 3 patients had a complex cardiac malformation and died of postoperative cardiac complications, 3 patients with multiple malformations (including cerebral abnormalities) died from sepsis, and only supportive care was given in 3 patients with a cloacal extrophy; 2 of these patients had trisomy 18 and one patient had Pallister Hall syndrome. Twenty-seven children were lost to follow-up, and parents of 6 did not enter the child in the follow-up program, resulting in 108 children included for this study. The baseline characteristics of the 33 children not seen in follow-up did not differ from those included in this study (not shown). The baseline characteristics of the 108 included children are shown in Table 1. Note the almost equal distribution of the type of malformation: 51% had a low malformation. At least one additional major comorbidity was documented in 46%. Other GI-disorders related to persisting growth problem were mainly esophageal atresia (n=9), and the need of a gastrostomy for serious feeding disorders (n=4). Twenty-two children did not undergo correcting surgery: 18 parents of 6 did not enter the child in the follow-up program, resulting in 108 children included for this study. The baseline characteristics of the 33 children not seen in follow-up did not differ from those included in this study (not shown). The baseline characteristics of the 108 included children are shown in Table 1. Note the almost equal distribution of the type of malformation: 51% had a low malformation. At least one additional major comorbidity was documented in 46%. Other GI-disorders related to persisting growth problem were mainly esophageal atresia (n=9), and the need of a gastrostomy for serious feeding disorders (n=4). Twenty-two children did not undergo correcting surgery: 18

<table>
<thead>
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<th>Table 1</th>
<th>Baseline characteristics.</th>
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<tr>
<td>Type of ARM a; n (%)</td>
<td>108</td>
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<tr>
<td>Low</td>
<td>55 (51)</td>
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<tr>
<td>High</td>
<td>53 (49)</td>
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<td>Male sex, n (%)</td>
<td>64 (59)</td>
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<tr>
<td>Absent or minor associated anomalies; n (%)</td>
<td>58 (54)</td>
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<td>At least 1 major associated anomaly; n (%)</td>
<td>50 (46)</td>
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<td>Specification of major anomalies b</td>
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<tr>
<td>Urogenital</td>
<td>28 (26)</td>
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<td>CNS</td>
<td>19 (18)</td>
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<td>Gastro-intestinal</td>
<td>14 (13)</td>
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<td>Cardiac</td>
<td>12 (11)</td>
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<tr>
<td>Pulmonary</td>
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<tr>
<td>Gestational age (weeks); mean (95% CI)</td>
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<td>Prematures c; n (%)</td>
<td>23 (21)</td>
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<tr>
<td>Birth weight (g); mean (95% CI)</td>
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<td>SGA; n (%)</td>
<td>8 (7)</td>
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<td>Surgically corrected d; n (%)</td>
<td>86 (80)</td>
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<td>Total surgical interventions, n; median (range)</td>
<td>3 (0–15)</td>
</tr>
<tr>
<td>Surgical interventions related to ARM, n; median (range)</td>
<td>1 (0–7)</td>
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</table>

Data shown are mean (95% confidence interval) or median (range), when appropriate. Abbreviations: ARM, anorectal malformations; CNS, central nervous system; SGA, small for gestational age; CI, confidence intervals.

a ARM classified parallel to Rintala as follows: low malformations were anal stenosis, covered anus, perianal fistula, and vestibular fistula. High malformations were rectourethral fistula, anal atresia without fistula, rectum atresia, and persisting cloaca.
b Percentages shown are of the total study sample. Because many children had more than 1 associated major anomaly, the total percentage exceeds 46%.
c Gestational age <37 weeks.
d 22 children had not undergone surgical correction of ARM: 18 had a low malformation requiring Hegar dilatation only, 4 had a high malformation and permanent colostomy.
had a low malformation requiring Hegar dilatation only; 4 had a high malformation for which a permanent colostomy was done. Four patients had a suspected syndromal diagnosis: 2 Cat eye syndrome, 1 Townes–Brocks syndrome, 1 Bardet–Biedl syndrome, they had all been included because the diagnosis was not confirmed.

2.1. Physical growth

In the children whose malformation was not part of a syndrome, SDS height was significantly lower than in the normative population at all contact moments (p<0.01, one sample t-test, Fig. 1). In total, 26 children (24%) had a persisting growth problem — 12 based on the SDS scores; 14 based on the THR. Growth failure was suspected in 12 other children (11%). Of the children with a persisting growth problem, 16 (62%) had at least one additional major comorbidity. Most of these comorbidities were of urogenital origin (n=10, 63%) and of CNS origin (n=10, 63%). Four of 30 children (13%) with major urogenital comorbidity had mildly impaired renal function: in 2 children serum creatinine levels were only elevated during urinary tract infections (maximum levels never exceeding 1 mg/dL), whereas both other children had one functioning kidney and chronically elevated creatinine (maximum levels never exceeding 0.8 mg/dL). One child with chronic renal dysfunction, who was also born small for gestational age, suffered from impaired growth.

SDS weight for height was impaired until 2 years of age (at 0.5 years p=0.015, at 1 year and 2 years p<0.01, one sample t-test). Also, SDS head circumference (measured until 2 years of age) was smaller than expected (p<0.01, one sample t-test). SDS height, SDS weight for height, and SDS head circumference did not differ significantly between children with a high malformation and children with a low malformation at any of the contact moments (independent samples t-test, data not shown). In contrast, the presence of additional major comorbidity significantly influenced height at all ages (0.5 and 1 year p<0.01, 2 and 5 years p=0.01, and 0.02, respectively, independent samples t-test), and weight for height until 1 year of age (p<0.01; Fig. 2).

In 54 children (50%) enterostomy was performed after birth. Nineteen of 26 children (73%) with a persisting growth problem had had an enterostomy, vs. 35/82 children (43%) without a persisting growth problem (p=0.007, Chi-Square test). Children with a persisting growth problem had a median (range) length of time with enterostomy of 529 (10 to 895) days vs. 470 (168 to 3622) days in the children without a persisting growth problem (p=0.403, Mann–Whitney test). Seven of 25 children with spinal anomalies had scoliosis; in four of them the severity of scoliosis might have impaired growth.

The median (range) number of operations in children with a persisting growth problem was 8 (1 to 29), vs. 6 (0 to 29) in the children without a persisting growth problem (p=0.147, Mann–Whitney Test). Two of 9 children who underwent major cardiac surgery had a persisting growth problem. The median (range) number of operations related to the anorectal malformation in children with a persisting growth problem was 3 (0 to 6), vs. 1 (0 to 8) in the children without (p=0.052, Mann–Whitney Test).

2.2. Development

Development had been evaluated in 102 children within the first 2 years of life. Seven of these had a syndromal
disorder. Thus, 95 children were included for analysis of development within the first two years of life.

2.3. Mental development

The mean (95% CI) mental developmental index (MDI) was not significantly lower than expected at 0.5, 1, and 2 years of age (Fig. 3). Five children (5%) had severe mental developmental delay; 8 children (8%) had mild mental developmental delay (i.e. between $-1$ and $-2$ SD).

IQ was tested in 25 of the 37 children (68%) who were seen at 5 years of age. Ten children were not tested for organizational reasons (they were seen after March 2011, when tests were only performed in case of suspected developmental delay); one child was visually impaired and one was severely retarded. The latter two were thought to have impaired intelligence. The baseline characteristics of the children tested did not differ from those not tested (data not shown).

The mean IQ (95% CI) was 102 (94 to 109). One child had a definitive cognitive delay (IQ $<70$; 4%), 4/25 children (16%) had a mild cognitive delay ($-1$ to $-2$ SD); and 20 (80%) had normal intelligence (IQ $>85$). The child that scored $<70$ (i.e. 60) had a high malformation and multiple major comorbidities. The MDI and IQ scores were neither significantly different between the children with a high malformation and those with a low malformation, nor between the children with additional major comorbidity and those without (data not shown).

2.4. Motor function development

At all contact moments within the first 2 years of life, the mean PDI of the 95 children tested was significantly lower than that of the normative population ($p<0.01$, one sample t-test; Fig. 3). Fourteen (15%) children showed severe motor developmental delay (PDI $<70$); 20 children (21%) had PDI scores between $-1$ and $-2$ SD. The PDI was significantly influenced neither by the type of malformation nor by the presence of additional major comorbidity (data not shown, Mann–Whitney test). Major CNS comorbidity was found in 5/14 children with a PDI $<70$ (4 tethered cord and 1 caudal regression syndrome).

At 5 years of age, reliable MABC results were obtained in 30/37 children. Four were not tested because of logistic reasons; these children were not suspected to have an impaired motor development. Three children who could not be tested had already physical therapy at home: 2 children suffered from severe neurological impairment; and 1 child was visually and auditorily impaired. Another four children who had physical therapy at home at time of assessment scored either normal (n = 3) or within the borderline range (n = 1). High type of malformation was significantly more frequent among the children not tested than among the children who did complete the MABC test ($p<0.01$, Mann–Whitney test). The other baseline characteristics did not differ between these two groups.

The total impairment score (TIS) distribution differed significantly from that of the normative population ($p = 0.043$, Chi-square test; Fig. 4), with significantly more children in the borderline range (7/29; 24%). A definitive motor problem was observed in only 2/29 children (7%). Many children had problems with the gross motor function (i.e. ball skills and balance skills); only few children had problems with the fine motor function (i.e. manual dexterity).

![Fig. 3](image-url) Development in children with an anorectal malformation until 2 years of age. Presented are the means (symbols) and 95% confidence intervals (whiskers) of the Bayley Developmental Scales 2–30 and the Bailey Scales of Infant Development-Second Edition-Dutch version. Circles represent mental developmental indexes, squares represent psychomotor developmental indexes. * $p<0.01$; tested with the one sample t-test (compared to the normative population).

![Fig. 4](image-url) Results of the Movement Assessment Battery for Children (MABC) at 5 years of age. Abbreviations: TIS, total impairment score; MD, manual dexterity; Ball, ball skills; BS, balance skills; Norm, normative population. Black represents the percentage of children that scored in the definitive motor problem range ($\leq p5$); gray represents that of the borderline range ($p6$–$p15$); white represents that of the normal range ($>p15$). *$p<0.01$, † $p<0.05$; tested with the Chi square test (compared to the normative population).
Three children were referred to a physical therapist based on their poor motor function performance.

2.5. Maximal exercise capacity

At 5 years of age, 25/30 children successfully completed the Bruce protocol. The mean (SD) SDS endurance time was −0.49 (1.17) (p=0.047, one sample t-test). Two children, both with a low malformation, scored <−2 SDS for the maximal exercise capacity. One child had 2 major comorbidities (none neurological) and the other had no significant comorbidity.

3. Discussion

This longitudinal evaluation of physical growth and development within the first 5 years of life in non-syndromal children with an anorectal malformation, which we believe is the first of its kind, points to risk for growth impairment, especially when the child has one or more major comorbidities. Mental development up to age 5 did not differ significantly from that in the normative population. More than a third showed impaired motor function development within the first 2 years of life; 15% of all children had a severe motor developmental delay; 21% had a mild motor developmental delay. At 5 years of age, 7% had a definitive motor function problem, while another 24% scored borderline. Accounting for the children that could not be tested because they were severely neurologically impaired; a total of 13% of the study sample has a definitive motor function problem at the age of 5. The maximal exercise tolerance was slightly, but significantly lower than in the normative population.

Analysis revealed that growth impairment was not related to the type of malformation (low or high). It was, however, related to the presence of comorbidity, notably of urogenital origin. Ginn-Pease and co-workers [2] found impaired growth in 9% of their study sample (n=34; mean age 11 years), while we found that 35% had a (possible) growth problem. There are two possible explanations for this difference. First, Ginn-Pease and co-workers described that most of the children did not have any chronic medical disorder, although they failed to provide a number. In our study, more than half of the children had at least one additional major comorbidity, which is in concurrence with the literature [21]. The comorbidity found in the children with growth impairment was mainly of urogenital origin. Renal function was normal in the majority of the patients. Only 4 children had mild renal dysfunction, of whom one had a persisting growth problem. Growth retardation resulting from a partial insensitivity to growth hormone, even if renal function is normal, has been reported in children with urological morbidity (i.e. vesicoureteral reflux) [22].

Secondly, Ginn-Pease and coworkers used another definition for growth impairment: they based their conclusions solely on height percentiles, while we also used the target height range. Using height percentiles only, we would have missed 14/26 children with a persisting growth problem (46%). Therefore, we advocate the use of the target height range, to avoid missing children at risk who could be adequately treated.

Growth retardation may result from either acute or chronic malnutrition. Recurrent hospitalizations and surgical procedures for additional major malformations may result in episodes of acute malnutrition. The chronic constipation with lack of appetite, which is inherent to anorectal malformations, may lead to chronic malnutrition. However, Rintala and coworkers described an up to 60% prevalence of constipation [1], and Chao and coworkers reported that healthy children with adequate treatment of functional constipation gained more height and weight than the non-responsive constipated children [23]. In addition, loss of appetite may be due to nausea and abdominal pain as a consequence of intensive bowel management. Because treatment of constipation is still an everyday challenge, pediatric surgeons and pediatricians should pay special attention to adequate bowel management and educating the parents and child. Further studies could make clear whether intensive bowel management in combination with tailor-made advice on daily caloric requirements may enhance physical growth in children with anorectal malformations. Screening all children with the STRONGkids score [24] – a nutritional risk screening tool – in combination with a practical algorithm (Fig. 5) can identify those in need for early referral to a dietician to prevent a persisting growth delay [25].

We found normal IQ in the children whose malformation was not part of a syndrome. Ginn-Pease and co-workers also found normal IQ in a cross-sectional cohort of 34 children with an anorectal malformation, mean age 11 years [2]. Hassink and co-workers reported a lower completed educational level in comparison to the normal Dutch population in a group of 58 adults with a corrected high malformation (median age 26 years, range 18 to 57 years) [3]. They suggested that fecal continence problems may have kept some patients away from school. The children in our study population were too young to experience such problems. Based on the scarce studies, we assume that in spite of normal mental capacity, underlying physical problems may give rise to educational problems. Both child and caregivers should receive adequate guidance, and additional guidance throughout the school career is needed.

We showed that non-syndromal children with anorectal malformations – especially those with additional major comorbidity – are at risk for motor function problems within the first 5 years of life. Based on previous observations by our group [6] in young children with abdominal wall defects, congenital diaphragmatic hernia, small intestinal anomalies, and esophageal atresia, we assume that factors indicative for severity of disease – e.g. the number of associated anomalies, but also duration of hospital admission and number of surgical interventions – also negatively influence
development of children with an anorectal malformation. As test results within the first years of life well predict development at 5 years of age [26], we advocate screening at a young age with early referral to a physical therapist, if indicated, to prevent delayed motor function development at a later age. This will improve the child’s physical activity and diminish the risk of impaired exercise tolerance.

These are the first results of a prospective longitudinal study in children with anorectal malformations. Regrettably, due to the small sample size at 5 years of age and the large number of possibly predictive factors, we could not perform a regression analysis to predict long-term morbidity. Future studies – preferably with a multicenter design – are needed to further define risk factors for delayed growth and development in non-syndromal anorectal malformation patients.

4. Conclusion

Non-syndromal children with an anorectal malformation are at risk for physical growth problems, especially when major comorbidity is involved. Thus, the nutritional status and bowel management should be optimized individually to prevent stunting. Mental development is generally not impaired, but attention should be paid to school performance and absenteeism secondary to persisting physical problems. Children with an anorectal malformation are at risk for gross motor function problems, especially those with additional major comorbidities. These findings are of importance in counseling parents. Longitudinal evaluation by a multidisciplinary team, including a pediatric surgeon, a pediatrician, a physical therapist, a dietician, a stoma nurse, and a pediatric urologist, is advocated during childhood and adolescence. In this way, optimal growth and development can be achieved.

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