Attention difficulties and physical dysfunction common in children with complex congenital malformations: a study of preschool children with VACTERL association

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ABSTRACT
Aim: Knowledge on the neurodevelopmental and physical function in children with vertebral defects, anorectal malformations, cardiac defects, tracheo-oesophageal fistula, renal and limb malformations (VACTERL) is scarce. We evaluated Swedish preschool children with VACTERL and identified whether they would need extra support in school.

Methods: From 2015 to 2017, we recruited children aged 5–7 with VACTERL association from the paediatric surgical centre at the University Children’s Hospital at Uppsala. Neurodevelopmental function was assessed by age-appropriate intelligence and visual and auditory attention tests, and the children’s behaviour and attention were observed by an experienced psychologist. Physical function was evaluated through parental interviews and examinations. Data on patient characteristics, including any surgery and anaesthesia, were extracted from medical records.

Results: Of the 13 eligible families, 10 agreed to participate. Intelligence was within the normal range for all children, but attention difficulties were found in eight of the children, requiring adjustments at school, and two of these were later diagnosed with attention deficit hyperactivity disorder. All children had physical dysfunctions that affected their daily nutrition, bowel or bladder functions.

Conclusion: Attention difficulties and physical dysfunction were common in Swedish preschool children aged 5–7 with VACTERL and they would need support and adjustments when they started school.

INTRODUCTION
VACTERL association is a complex condition of congenital malformations that coexist in a single patient and the acronym stands for vertebral defects, anorectal malformations, cardiac defects, tracheo-oesophageal fistula, renal anomalies and limb abnormalities. At least three of these conditions need to be present for a VACTERL diagnosis (1). Various sequelae in adult patients with VACTERL association have been described in the literature, such as dysphagia, gastro-oesophageal reflux, respiratory disorders, bowel dysfunction and sequelae of vertebral, cardiac, renal and limb malformations (1–3). However, studies of children with VACTERL association are scarce. Reports on the physical outcomes in such children have been limited to the sequelae of a single malformation (2,4).

In order to survive, most children with VACTERL association require surgery during the first days of life and often undergo multiple operations during infancy (1). Several studies have reported an association between

Key notes
- We evaluated 10 children aged 5–7 with vertebral defects, anorectal malformations, cardiac defects, tracheo-oesophageal fistula, renal and limb malformations and assessed whether they would need extra support at school.
- Intelligence was within the normal range for all children, but attention difficulties were found in eight children and two were later diagnosed with attention deficit hyperactivity disorder.
- All children had physical dysfunctions that affected their daily nutrition, bowel or bladder functions.
surgery during infancy and neurodevelopmental dysfunction (5). The risk factors that have been described were multiple congenital anomalies, low birth weight, repeated surgery and long hospital stays (6). In animal studies, adverse effects of general anaesthesia on the developing brain have been found and most pronounced in young animals after longer and repeated exposure but corresponding effects on the infant brain are debated since the findings are difficult to translate to humans (5).

Knowledge on the neurodevelopmental outcomes of children with VACTERL association is scarce, but there have been reports on adverse neurodevelopmental outcomes in children with single malformations (6,7).

The aim of this study was to evaluate neurodevelopment and physical functions in a cohort of Swedish preschool children aged 5–7 with VACTERL association and to identify if these children would need extra support at school.

PATIENTS AND METHODS
Participants
From 2015 to 2017, we recruited children aged 5–7 with a diagnosis of VACTERL association from a tertiary paediatric surgical centre at the University Children’s Hospital, Uppsala. The hospital serves a patient population of approximately two million people from the middle and northern parts of Sweden. A letter that described the study was sent to the parents of 13 eligible children inviting the families to participate in the study and 10 agreed to take part. Written informed consent was obtained from both parents.

Method and data collection
The children were evaluated in the regional habilitation centre of the hospital over a three-day period by a psychologist and a paediatric neurologist.

Neurodevelopmental evaluation
If the children were five or six years of age we used the Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV) (8) to assess their neurodevelopmental performance. The Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) was used for those who were seven years old (9). From the subtests in the WPPSI-IV five different index scores were constructed and four were constructed from the subtests in the WISC-IV. A composite score of the full-scale intelligence quotient (IQ) was obtained from parts of the different scales. We grouped together the index and composite scores, which had a mean of 100 and standard deviation (SD) of 15 in material based on the SD intervals of the general Scandinavian population. The groups were defined by these composite scores as average (93–107), low average (85–92), borderline (70–84) and extremely low (<70).

The visual attention and auditory attention tests from Developmental Neuropsychological Assessment, commonly known as NEPSY (10), were used for four children, namely numbers 7–10. An experienced psychologist observed the children’s behaviour during testing and this included focused, divided, shifting and sustained attention, signs of inattention, observation of impulse control and levels of activity. The observations included whether the tester could catch the child’s attention, the child’s ability to follow visual or verbal instructions and whether the child could focus on a task and perform it consistently. Their level of impulse control was assessed by observing their ability to concentrate without being distracted by objects or sounds unrelated to the tests. Signs of possible hyperactivity were evaluated by observing their ability to sit still without touching or moving objects around, making noises or moving around. Before the evaluations were carried out we obtained information about how well the children functioned in their preschool from their teachers.

Physical evaluation
The first author (A-MK) interviewed the parents by telephone shortly before the evaluation to gather information about the child’s health and their physical functions, including any problems, in daily life.

The paediatric neurologist interviewed the parents about the child’s actual physical functions and medical problems and performed a physical and neurological investigation, including weight and height. Data were collected from the medical records, including information about the child’s gestational age, their APGAR scores and their weight at birth, former and present physical function, growth and number of operations and episodes of general anaesthesia.

All the results and recommendations from the evaluations were conveyed to the parents in the first instance. We then held a video conference to communicate the findings to the paediatrician and nurse responsible for the child at their local hospital and representatives of their present preschool and future school.

Data analysis
Categoric data are presented with counts. Descriptive analysis of the numeric results was performed by calculating the medians and ranges. Deviations in weight and height are presented as standard deviations, with calculated medians and ranges. Results from the two age-appropriate Wechsler tests are grouped with text descriptions according to standard deviations in the general Scandinavian population. Due to the low number of participants, no percentage calculations or significance testing of the results were performed.

Ethics
The study was approved by the Regional Ethical Review Board in Uppsala (registration number 2015/264). The voluntary nature of the participation was emphasised to the parents.

RESULTS
The patient characteristics are demonstrated in Table 1. The study group consisted of 10 children (six boys) with a
The median age of 5.71 (range 4.90–7.25) years. The median gestational age at birth was 35.5 weeks, and the median birth weight was 2290 g. All the children underwent major surgery within the first three days of life due to congenital heart disease, oesophageal atresia or anorectal malformations.

Surgeries and anaesthesias
The number of completed operations and episodes of anaesthesia each child went through before they were evaluated are demonstrated in Figure 1. The median number of major operations requiring postoperative in-patient care prior to our evaluation was 3.5 (range 1–9), and the episodes of anaesthesia varied between three and 52, with a median of seven.

Neurodevelopmental evaluation
Results from the WPPSI-IV and WISC-IV evaluations are presented in Table 2. The children’s full-scale IQ was within the normal range for all 10 children: five were average, three were low average and two were borderline. The verbal comprehension index was below average in four children, borderline in two and extremely low in two. The scores for the visual–spatial and processing speed indexes were borderline in three children. Furthermore, borderline results in both fluid and working memory indexes were found in two children.

The results from the observations of attention are presented in Table 3. We used the visual attention and auditory attention tests for four children, but the results were impossible to calculate in three of them, due to the attention problems described below. Observing the children in test situations for between two to five sessions showed that eight of the 10 children had attention difficulties. These emerged as problems in focused, divided, shifting and sustained attention, as well as inattention to a task, hyperactivity or difficulties with impulse control (Table 3). Of these eight children, five had borderline or extremely low scores in the verbal and, or, visual–spatial index tests. After evaluation, two of the children with attention difficulties were diagnosed with attention deficit hyperactivity disorder (ADHD) following extended investigations.

Physical evaluation
All of the children were found to have normal motor function and the only neurological deviation was a minor finding of abducens nerve palsy in one child. We noted that three of the children were underweight (<–2 SD) and four had short stature (<–2 SD).
The children’s parents reported several problems with physical function in the children’s daily life and these are presented in Figure 2. The majority, nine of the 10, had nutritional problems and these manifested themselves as selective or slow eating or eating too quickly and risking food obstruction. Gastrostomy was used in one of the children. Bowel dysfunction was reported in seven out of the 10 children, including constipation, and five
experienced faecal soiling. The bladder dysfunction issues in five children with anorectal malformations comprised of urinary incontinence or passing urine into a nappy. In one child this was continuously and in three children it was intermittent. Furthermore, one child depended on continuous suprapubic drainage. Reduced physical strength was described in four of the children: two had previously undergone cardiac surgery and two had asthma or frequent respiratory infections. Surgery for a tethered spinal cord was previously performed in two children and another two had symptoms of pain in the back and legs requiring further investigations to see if they had this condition.

Recommendations of support
All the children we included needed some cognitive or physical adjustments and assistance in school. The children with attention difficulties needed distinct instructions and structured measures like short working periods, breaks, varied school tasks and reminders. Support was recommended during meals and for toilet visits, and some of the children needed full-time rather than part-time support.

DISCUSSION
This was the first report to describe the neurodevelopmental and physical outcomes of preschool children with VACTERL association. All the children had physical dysfunction. Intelligence was within the normal range, but most of the children had obvious difficulties paying attention and two of them were later diagnosed with ADHD. We found that all children in the study group would need extra support and adjustments when they went to primary school.

Previous results on the neurodevelopmental outcomes in children born with congenital malformations were difficult to compare to the present study as they were restricted to evaluating children with single malformations, whereas this study covered children with at least three malformations. Moreover, previous reports have produced conflicting results. All the children in our study group were exposed to at least two risk factors for neurodevelopmental dysfunction, including multiple anomalies and neonatal surgery (6).

We found that two of the 10 children in our study had an IQ of below 1 SD and this was similar to other studies that have reported 25% in children with congenital diaphragmatic hernia (11), 22.4% in congenital heart disease (12) and 16% in the general population (8). Mental retardation, which was defined as having an IQ of less than 70, has been reported in 21% (13), 14% (11) and 4.8% (14) of children born with various noncardiac malformations. In contrast, Walker et al. found that patients with oesophageal atresia demonstrated normal neurodevelopment at the age of three (15). Another study of children born with gastroschisis showed no significant differences to the general population at a median age of 10 years (16).

When it came to the verbal comprehension index in our study, four children scored below 1 SD, compared to 31% (11) and 10% (16) in studies that examined children with noncardiac anomalies. In addition, significantly lower median scores for verbal comprehension have been reported in children with cardiac malformations than in the general population (12). Furthermore, scores below 2 SD were found in two children in our study group, which were higher than the 11% (11) and 2.5% (16) reported by studies of children with noncardiac congenital anomalies.

Our study found that eight of the ten children had attention difficulties. These findings were supported by the fact that it was impossible to calculate the results of the visual attention and auditory attention tests in three of the four children that underwent these tests. Their parents also confirmed the difficulties that we identified. It was clear that these children would probably struggle with the transition to primary school as they were already becoming tired because of the greater need to focus at preschool. The increasing demands of starting school might make this situation worse and these children would require special assistance and adjustments in school.

Previous studies of children born with various congenital malformations have reported attention difficulties, such as significantly worse scores in working memory in 41% (17) and sustained attention levels that were lower than the
general population (18,19). One study also found that their risk of having high-risk scores for inattentiveness and hyperactivity were three to four times higher than the general population (20). In our study group, two children were later diagnosed with ADHD. One study that included children with colorectal malformations found that 12% had been diagnosed with ADHD (18), while the international prevalence of ADHD has been reported to be approximately 5–7% in children and adolescents in the general population (21).

The impact of general anaesthesia on future neurodevelopmental function is debated. A randomised trial using spinal versus general anaesthesia less than one hour in children having surgery for hernia repair (22) and a large sibling cohort (23) did not find any differences in neurodevelopmental outcomes between exposed and unexposed children. On the other hand, Castellheim et al. reported from a twin study that exposure to anaesthesia and surgery may be a risk factor for ADHD traits (24). For our group of children, these results are difficult to compare since the exposures to anaesthesia and surgery usually occur earlier than reported studies, namely in the first few days of life, and often last longer than one hour. Even though the episodes of anaesthesia were below median in the children with age-adequate attention and above median in those diagnosed with ADHD we were not able to draw any conclusions about the correlation between the number of episodes of anaesthesia and attention difficulties due to our small study group.

All the children in the current study had physical dysfunctions that affected their daily lives and most of them needed some assistance at meal times. Interestingly, difficulties were not just seen in children with oesophageal atresia, who often suffer from dysphagia (2). Children who are slow and arrive late in the school canteen for their lunch, and have difficulties concentrating on what they need to do, may also have problems with an insufficient intake of calories during school days. Therefore, it is important to provide these children with some extra time for meals and adult support to ensure that they eat enough.

All seven of the children born with anorectal malformations in our study group needed treatment for bowel dysfunction. One study of children with anorectal malformations showed that patients demonstrated a lower quality of life with regard to emotional, social and school domains than controls without this condition (25). Making teachers and teaching assistants aware of the signs of leakage is crucial if these children are to avoid social stigmatisation.

In the study group, two of the children with an anorectal malformation had been treated for a tethered spinal cord and two other children with this condition had displayed symptoms that suggested they might also receive this diagnosis after further investigations. O’Neill et al. (26) and Kuo et al. (27) reported a high prevalence of tethered spinal cords in children with VACTERL association. It is important that the treating paediatrician observes the signs and symptoms of this condition and initiates investigations.

There is no formal follow-up programme to assess both the neurodevelopmental and the physical functions of children with VACTERL association in Sweden. However, a programme is available in the Netherlands that evaluates physical, developmental and psychosocial functions in children with congenital anomalies at various intervals up to the age of 18 years (28). In Sweden, children who are born premature and small for their gestational age, and who also meet certain other criteria, are followed up by multidisciplinary teams until they are 5.5 years of age (29). In addition, a Norwegian guideline has been developed for a similar follow-up programme for children born with congenital heart disease (30). For the group of children with VACTERL association as well as other multiple congenital anomalies, it is imperative to implement neurodevelopmental screening in the follow-up programme by at minimum using questionnaires to parents and teachers to identify those who are at risk for dysfunction and in need of further psychological investigations.

Future research on this group will probably be limited to observational prospective studies since early surgery is inevitable and requiring general anaesthesia. To gain knowledge from larger cohorts the use of a national or when available international quality register is essential, into which neurodevelopmental outcomes could be registered in addition to physical data such as the type of malformations and their outcomes, together with type and length of episodes of anaesthesia and surgery.

The strengths of the present study were that it was the first evaluation of neurodevelopmental and physical outcome in preschool children aged 5–7 with VACTERL association and all the children had similar previous experiences: major surgery during the first few days of life, repeated treatment and physical dysfunction. Moreover, the evaluations were carefully carried out by professionals who were very experienced in performing such assessments in children with various diagnoses, neurodevelopmental conditions and ages.

The limitations of the study were the small sample size and a possibility of selection bias, because the parents of three patients with poorer or better outcomes may have declined to participate.

CONCLUSION
Attention difficulties and physical dysfunction were common in preschool children aged 5–7 with VACTERL association and it was clear that they would all need extra support and adjustments when they started school. It is essential to carry out neurodevelopmental and physical evaluations of children with VACTERL before such children start primary school so that any additional support needs can be identified.

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CONFLICT OF INTEREST
The authors have no conflict of interest to declare.

References