

## ORIGINAL ARTICLE

# Swedish cohort study found that half of the girls with shunted hydrocephalus had precocious or early puberty

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## Abstract

**Aim:** We aimed to evaluate the occurrence of, and risk factors for precocious and early puberty in a retrospective cohort study of girls with shunted infantile hydrocephalus.

**Methods:** The study population comprised 82 girls with infantile hydrocephalus, born between 1980 and 2002, and treated with a ventriculoperitoneal shunt. Data were available for 39 girls with myelomeningocele and 34 without. Medical records were analysed regarding clinical data and timing of puberty. Precocious and early puberty was defined as the appearance of pubertal signs before 8 years and 0 months and 8 years and 9 months, respectively.

**Results:** Median age at last admission was 15.8 years (range 10.0–18.0). In total, 15 girls (21%) had precocious puberty, and another 21 (29%) had early puberty. Three or more shunt revisions had been performed in 26/36 girls with early or precocious puberty and in 3/37 girls without ( $p=0.01$ ). The number of shunt revisions correlated negatively with age at the start of puberty in the girls with myelomeningocele (Spearman's correlation coefficient =  $-0.512$ ,  $p=0.001$ ).

**Conclusion:** Girls with shunted infantile hydrocephalus have a high risk of precocious or early puberty. Repeated shunt revisions seemed to be associated with early puberty.

## KEYWORDS

girls, hydrocephalus, myelomeningocele, puberty, ventriculoperitoneal shunt

## 1 | INTRODUCTION

Hydrocephalus can be defined as an increase of cerebrospinal fluid within the skull.<sup>1</sup> If untreated, it results in ventricular dilatation and high intracranial pressure. Insertion of a ventriculoperitoneal shunt reduces intracranial pressure and decreases the risk of brain damage.

Hydrocephalus may appear prenatally, perinatally or postnatally as a consequence of Chiari- or other cerebral malformations, cerebral haemorrhages, infections or tumours.<sup>1</sup> With infantile hydrocephalus

we mean hydrocephalus, necessitating shunt operation, present at birth or during the first year of life.

Precocious or early puberty has been reported in patients with hydrocephalus.<sup>2–5</sup> Kaijser et al. investigated 90 children (46 female) with shunted hydrocephalus without spina bifida. They found that four girls and four boys had precocious puberty.<sup>6</sup> In a Swedish prospective population-based study, 68 term children (40 male) with infantile hydrocephalus were followed up until a mean age of 11.25 years. Precocious puberty was reported in five girls and six

Abbreviation: TANNER STAGE B2, Breast bud palpable under the areola

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boys.<sup>7</sup> In a cross-sectional study Löpönnen et al evaluated pubertal development and peripheral concentrations of gonadotropin and sexual hormones in 114 patients (62 male), 5–20 years, with shunted infantile hydrocephalus, and 73 age-matched healthy controls.<sup>8</sup> They found that both girls and boys with hydrocephalus had advanced pubertal development. The girls had significantly earlier time for menarche in comparison both with their mothers and controls. The prepubertal patients had higher sexual hormones than the controls. Three girls and two boys had precocious puberty.<sup>8</sup>

Early puberty was also demonstrated in patients with myelomeningocele, particularly in those with associated hydrocephalus.<sup>9–11</sup> In a retrospective analysis Trollmann et al. investigated growth and pubertal development in 109 patients: (52 male), median age 8.9 years, with myelomeningocele and hydrocephalus. They found that 5/27 (19%) of pubertal girls had precocious puberty.<sup>12</sup> In a retrospective population-based study on 32 girls with myelomeningocele we found that 20 girls had early puberty. We also pointed out that a perinatal increase in intracranial pressure was a strong predictor of early puberty in these girls.<sup>10</sup>

In general, precocious and early puberty is more common in girls than in boys.<sup>13</sup> In a population-based retrospective study of boys with myelomeningocele, early puberty was found in 21%. However, it was also observed that data on pubertal development in medical records were missing more often for the boys than for the girls.<sup>14</sup>

Central precocious puberty is caused by the activation of the hypothalamic–pituitary–gonadal axis.<sup>15</sup> Precocious and early puberty in girls is usually idiopathic but may occur as a result of cerebral lesions and genetic syndromes.<sup>16</sup> Even though the detailed mechanisms behind the start of puberty are not fully known, increased hypothalamic production of kisspeptins appears critical for the process.<sup>17</sup>

Little information is available on the mechanism behind the effect of increased intracranial pressure on the hypothalamic–pituitary–gonadal axis, leading to early or precocious puberty.<sup>18,19</sup>

Most earlier studies of children with hydrocephalus of other causes than myelomeningocele were performed on selected patients.<sup>4–7,20,21</sup> It is therefore difficult to draw conclusions regarding occurrence of precocious or early puberty, and possible risk factors for these conditions.

The aim of this study was to define the occurrence of precocious and early puberty in female patients with infantile hydrocephalus operated with a ventriculoperitoneal shunt. To the best of our knowledge, this is the first population-based investigation on unselected patients. We also aimed to identify factors associated with early puberty.

## 2 | PATIENTS AND METHODS

The present investigation was a retrospective cohort study. The study population comprised all 82 girls with infantile shunted hydrocephalus, born between 1980 and 2002, in our catchment area of about 2 million inhabitants. There were 39 girls with and 42

### Key Notes

- Precocious and early puberty has been demonstrated in girls with hydrocephalus, but population-based studies are lacking.
- Precocious puberty was found in 15/73 girls (21%) and another 21/73 (29%) had early puberty.
- All girls with shunted infantile hydrocephalus should be routinely monitored for pubertal development.

without myelomeningocele. The patients had been admitted to the Department of Pediatric Surgery at Uppsala University Children's Hospital for insertion of a ventriculoperitoneal shunt.

Medical record data, sufficient for evaluation of pubertal development, were available for 73 girls: 39 with myelomeningocele and 34 without. The cause of hydrocephalus in the non-myelomeningocele group was perinatal intraventricular haemorrhage, cerebral malformation, and cerebral infection for 17, 11 or three girls, respectively. The cause was unknown for the three girls.

Medical records from hospitals and paediatric habilitation centres were reviewed by one of the authors (MD). Data on age and intraventricular pressure at shunt insertion were collected, as well as information on medical, and functional problems. All data on puberty in the medical records were collected. Puberty was assessed in connection to regular follow-up at paediatric outpatient clinics. The assessments were performed according to Tanner stages by paediatric neurologists.<sup>22</sup> In addition, data on weight and length at birth and up to 15 years of age were collected. Body mass index was calculated, and converted to standard deviation scores.<sup>23</sup> Early puberty was defined as the appearance of pubertal signs before 8 years and 9 months.<sup>24</sup> Precocious puberty, representing a subgroup of early puberty in this study, was defined as the appearance of pubertal signs before 8 years of age. The appearance of Tanner stage B2 was not recorded in the medical records for the three girls. For these patients, the age at onset of pubertal growth spurt, defined by the intersection of the prepubertal and pubertal linear growth trajectories, was used.<sup>25</sup>

### 2.1 | Statistics

Continuous variables are presented as median and ranges, and categorical variables as numbers or proportions. Statistical differences were calculated by means of Fisher's exact test for categorical variables. For continuous variables, Student's *t*-test for independent variables was used for parametric variables, and the Mann–Whitney *U* test for non-parametric variables. Calculation of Spearman's correlation coefficient was used to reflect the relationship between age at onset of puberty, and the number of shunt revisions for girls with myelomeningocele. The statistical analysis was performed, using SPSS, statistics, version 28 (IBM Corp, New York, USA).

## 2.2 | Ethics

The study was approved by the Regional Ethical Review Board of Uppsala (2015/085). Informed consent was not considered necessary since no information on the identity of the individual patients could be obtained from the data presented.

## 3 | RESULTS

### 3.1 | Clinical characteristics

As can be seen in Table 1 most of the children in the study were non-functional ambulators, meaning they could not walk. Many patients were diagnosed with mental retardation and epilepsy. One-third were born prematurely. Five of these were born before 28 weeks of gestation.

Shunt operations were performed before 14 days for 16 girls (22%), between 14 and 100 days for 33 girls (45%), and after 100 days for 24 girls (33%).

The children without myelomeningocele were more often functional ambulators than those with myelomeningocele (Table 1). Premature birth was recorded for 17 of the children without myelomeningocele (50%). Shunt insertions were performed at an age of more than 100 days for 17 (50%) of the children without myelomeningocele compared with seven (18%) of the children with myelomeningocele, ( $p=0.006$ ). Eight girls with myelomeningocele (21%) and seven of those without myelomeningocele (21%) had undergone at least three shunt revisions.

### 3.2 | Occurrence of precocious and early puberty

In the total material, 15 girls (21%) had precocious puberty, and another 21 girls (29%) had early puberty. Median age at pubertal onset was 8 years and 9 months, range of 5–13 years.

Early puberty was found in 21 (54%) of the girls with myelomeningocele, and in 15 (44%) of those without. Precocious puberty was

found in 7 (18%) and 9 (26%) of the children with and without myelomeningocele, respectively.

### 3.3 | Factors associated with early puberty

As shown in Table 2, more children with precocious or early puberty had undergone three or more shunt revisions, as compared to those with normal puberty. Also, more of those with precocious or early puberty were unable to walk. There were no differences between the patients with early and those with normal puberty with respect to gestational age, weight, height, or body mass index up to 6 years of age. Neither were any differences found regarding, intracranial pressure, nor for the time of shunt insertion.

In the group of children with myelomeningocele, those with early puberty had undergone more shunt revisions, than those with normal puberty (median 2.0, range 0–5 versus median 0.5, range 0–2,  $p=0.028$ ). The number of revisions correlated negatively with age at the start of puberty (Spearman's correlation coefficient =  $-0.512$ ,  $p < 0.001$ ) (Figure 1). No risk factors associated with precocious or early puberty were found in the children without myelomeningocele.

### 3.4 | Treatment of precocious and early puberty

Treatment with gonadotropin-releasing hormone analogue was given to 33 girls (45%): 22 with and 11 without myelomeningocele. Five girls with myelomeningocele were treated even though they did not fulfil the criteria for early puberty.

## 4 | DISCUSSION

To the best of our knowledge, the present study is the first to report pubertal development in a large, and unselected population-based cohort of girls with infantile hydrocephalus.<sup>19</sup> The main findings

TABLE 1 Clinical data for girls with and without myelomeningocele.

Variable	Total	MMC <sup>a</sup> (n = 39)	Non-MMC (n = 34)	p-value <sup>b</sup>
Gestational age weeks, median (min–max)	37.5 (23–43)	38.0 (29–42)	37.5 (23–43)	NS
Birth weight grams, median (min–max)	3060 (675–4475)	3338 (1295–4456)	3060 (675–4475)	0.013
Age at the insertion of the VP <sup>c</sup> shunt, days	31 (1–2100)	21 (1–180)	31 (1–2100)	<0.001
Intracranial pressure cm H <sub>2</sub> O, median (min–max)	17.0 (5.5–43.0)	16.0 (5.5–26.0)	17.0 (5.5–43.0)	NS
Age at last admission, years, median (min–max)	15.8 (10.0–18.0)	15.8 (10.0–18.0)	15.8 (10.0–18.0)	NS
Non-functional ambulation, n (%)	42 (58)	30 (77)	12 (35)	<0.001
Mental retardation, n (%)	28 (38)	14 (36)	14 (41)	NS
Epilepsy, n (%)	19 (26)	7 (18)	12 (35)	NS
Cerebral palsy, n (%)	10 (14)	0 (0)	10 (30)	<0.001

<sup>a</sup>Myelomeningocele.

<sup>b</sup>Comparison between girls with and without MMC.

<sup>c</sup>Ventriculoperitoneal.

TABLE 2 Girls with precocious or early puberty compared to girls with normal puberty onset.

Variables	Early puberty (n = 36)	Normal puberty (n = 37)	p-value
Gestational age weeks, median (min–max)	38 (23–42)	37 (25–43)	NS
Birth weight grams, median (min–max)	3315 (675–4475)	3032 (700–4340)	NS
Insertion VP <sup>a</sup> shunt days, median (min–max)	42 (1–1500)	28 (1–2100)	NS
Intracranial pressure cm, median (min–max)	17.3 (10.0–40.0)	17.0 (5.5–43.0)	NS
Age at last admission years, median (min–max)	15.9 (10.0–18.0)	15.7 (10.0–18.0)	NS
No. of shunt revisions, median (min–max)	2 (0–5)	1 (0–7)	NS
Non-functional ambulator, n (%)	26 (72)	16 (43)	0.018
Mental retardation, n (%)	16 (44)	12 (32)	NS
Epilepsy, n (%)	12 (33)	7 (19)	NS
Cerebral palsy, n (%)	6 (17)	4 (11)	NS
Shunt revisions, 3 or more, n (%)	12 (33)	3 (8)	0.01

<sup>a</sup>Ventriculoperitoneal.

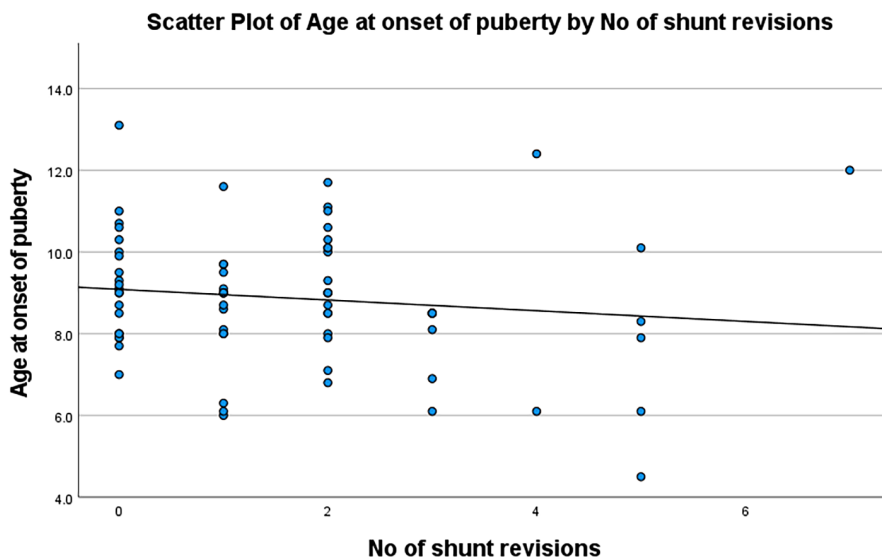


FIGURE 1 Number of shunt revisions in relation to age at the start of puberty for children with MMC.

were the high occurrence of precocious or early puberty, and the association of early puberty and repeated shunt revisions.

We found a high occurrence of precocious or early puberty among the patients studied. The proportion of precocious or early puberty in our material was 50 per cent. This figure is higher than those reported in previous studies.<sup>2–9</sup> This may be due to differences in study populations.

The number of shunt revisions in the children with myelomeningocele was positively associated with early puberty, a finding in agreement with previous data reported by Löppönen et al. in their study of boys and girls.<sup>3</sup> The authors speculated that even small variations in intracranial pressure may affect the activation of the hypothalamic–pituitary–gonadal axis.<sup>3</sup> However, in contrast to our own results in a previous study of girls with myelomeningocele,<sup>10</sup> early high intracranial pressure was not associated with precocious, or early puberty.

Neither timing nor intracranial pressure at shunt insertion were associated with early puberty in the total study sample. However, it is difficult to draw conclusions from these results, since the underlying

causes of hydrocephalus were heterogeneous. In addition, the lack of data from nine children with myelomeningocele might influence the results.

Patients with precocious puberty are at risk of short stature due to premature closure of the epiphyses.<sup>16</sup> In addition, psychosocial consequences of early maturation must be considered.<sup>26</sup> Gonadotropin-releasing hormone analogues are used for the treatment of central precocious puberty, halting physical as well as skeletal maturation, and postponing menarche.<sup>16,27,28</sup> The majority of the patients with precocious or early puberty, with or without hydrocephalus, obtained such treatment. In addition, in order to postpone menarche four girls with the start of puberty at 9 years and one at 9 years and 7 months were also treated.

Even though treatment with gonadotropin-releasing hormone analogues is generally considered safe,<sup>27,28</sup> prolonged treatment may result in weight gain and impaired bone mineralization. These effects are particularly disadvantageous for non-ambulant girls and should be kept in mind when treatment is considered, as well as during follow-up of treatment.

Since patients with hydrocephalus are already afflicted by their condition, early pubertal maturation may present an additional burden.<sup>28</sup> Girls with a shunted hydrocephalus should therefore be routinely monitored for linear growth and physical development, in order to identify signs of precocious or early puberty. This can be ascertained by determining age at Tanner stage B2, and by defining the age at the intersection of the prepubertal and pubertal linear growth trajectories.<sup>25</sup>

One strength of the study is that it represented all children with shunted hydrocephalus in our referral area, born during a 22-year period. Another strength is that it was possible to evaluate pubertal development in a high proportion of the patients (73/82).

In addition, medical data concerning the prenatal, perinatal, and postnatal periods, were collected for all children. The lack of pubertal data in the records of nine patients without myelomeningocele represents a study limitation. This may be due to the absence of pubertal signs, or incomplete physical investigation. Even though the age at onset of pubertal growth was used to identify the start of puberty only in three girls, the difficulty of measuring height in patients with non-functional ambulation may represent another limitation.

## 5 | CONCLUSIONS

The major finding in this population-based study was the high frequency of precocious or early puberty, found in the girls with shunted infantile hydrocephalus. Girls with myelomeningocele and repeated shunt revisions are at particular risk of precocious or early puberty.

Early detection of precocious or early puberty is important, since it may add another burden in terms of practical, and psychological problems for girls with shunted hydrocephalus. When indicated, this condition may be alleviated by postponing the pubertal development, by treatment with gonadotropin-releasing hormone analogues.

### AUTHOR CONTRIBUTIONS

**Margareta Dahl:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; validation; visualization; writing – original draft; writing – review and editing. **Lemm Proos:** Conceptualization; data curation; funding acquisition; investigation; methodology; resources; software; visualization; writing – original draft. **Kai Arnell:** Data curation; investigation; methodology; software; writing – original draft. **Jan Gustafsson:** Conceptualization; data curation; formal analysis; investigation; methodology; resources; software; validation; writing – original draft; writing – review and editing.

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### CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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### REFERENCES

1. Tully HM, Dobyns WB. Infantile hydrocephalus: review of epidemiology, classifications and causes. *Eur J Med Genet.* 2014;57(8):359-68.
2. Hochhaus F, Butenandt O, Schwarz HP, Ring-Mrozik E. Auxological and endocrinological evaluation of children with hydrocephalus and/or meningomyelocele. *Eur J Pediatr.* 1997;156:597-601.
3. Löppönen T, Saukkonen AL, Serlo W, Tapanainen P, Ruokonen A, Knip M. Accelerated pubertal development in patients with shunted hydrocephalus. *Arch Dis Child.* 1996;74:490-6.
4. Cholley F, Trivin C, Saint-Rose C, Souberbielle JC, Cinalli G, Brauner R. Disorders of growth and puberty in children with non-tumoral hydrocephalus. *J Pediatr Endocrinol Metab.* 2001;14(3):319-27.
5. De Luca F, Muritano M, Rizzo G, Pandullo E, Cardia E. True precocious puberty: a long term complication in children with shunted non-tumoral hydrocephalus. *Helv Paediatr Acta.* 1985;40:467-72.
6. Kaiser G, Ruedeberg A. Endocrinological disorders in shunted hydrocephalus. *Z Kinderchir.* 1989;44(suppl 1):16-7.
7. Fernell E, Hagberg B, Hagberg G. Epidemiology of infantile hydrocephalus in Sweden: a clinical follow-up study in children born at term. *Neuropediatrics.* 1988;19:135-42.
8. Löppönen T, Saukkonen AL, Selo W, Lanning P, Knip M. Slow prepubertal growth but early pubertal growth in children with hydrocephalus. *Pediatrics.* 1995;95:917-23.
9. Meyer S, Landau H. Precocious puberty in myelomeningocele patients. *J Pediatr Orthop.* 1984;4:28-31.
10. Proos LA, Dahl M, Ahlsten G, Tuvemo T, Gustafsson J. Increased intracranial pressure and prediction of early puberty in girls with myelomeningocele. *Arch Dis Child.* 1996;75:42-5.
11. Green SA. Growth and sexual development on children with meningomyelocele. *Eur J Pediatr.* 1985;44:146-8.
12. Trollmann RM, Strehl E, Darr HG. Precocious puberty in children with myelomeningocele: treatment with gonadotropin-releasing hormone analogues. *Dev Med Child Neurol.* 1998;40:38-43.
13. Bridges NA, Christopher JA, Hindmarsh PC, Brook CG. Sexual precocity: sex incidence and aetiology. *Arch Dis Child.* 1994;70:116-8.
14. Proos LA, Tuvemo T, Ahlsten G, Gustafsson J, Dahl M. Increased perinatal intracranial pressure and brainstem dysfunction predict early puberty in boys with myelomeningocele. *Acta Paediatr.* 2011;100:1368-72.
15. Brito VN, Canton A, Seraphim CE, et al. The congenital and acquired mechanisms implicated in the etiology of central precocious puberty. *Endocr Rev.* 2023;44:193-221.
16. Bradley SH, Lawrence N, Steele C, Mohamed Z. Precocious puberty. *BMJ.* 2020;368:165-97.
17. Cintra RG, Wajnsztejn R, Trevisan CM, et al. Kisspeptin levels in girls with precocious puberty: a systematic review and meta-analysis. *Horm Res Paediatr.* 2020;93:589-98.
18. Abdolvahabi RM, Mitchell JA, Diaz FG, McAllister JP. A brief review of the effects of chronic hydrocephalus on the gonadotropin releasing hormone system: implications for amenorrhea and precocious puberty. *Neurol Res.* 2000;22:123-6.
19. McAllister JP, Abdolvahabi RM, Walker ML, Mitchell JA, Jones HZ. Effects of congenital hydrocephalus on the hypothalamic

- gonadotrophin-releasing hormone system. *Neurosurg Focus*. 2007;22(4):E4-E10.
20. Olivan-Gazalvo G, Calatayud-Maldonado V. Coexistence of central precocious puberty and intraventricular arachnoidal cyst. A brief literature update. *Iberoamerican J Med*. 2021;3:65-70.
  21. Villani R, Tomei G, Gaini SM, Grimoldi N, Spagnoli D, Bello L. Long-term outcome in aqueductal stenosis. *Childs Nerv Syst*. 1995;11(3):180-5.
  22. Tanner JM. *Growth at Adolescence*. 2nd ed. Springfield, Ill; 1962.
  23. He Q, Albertsson-Wikland K, Karlberg J. Population-based body mass index reference values from Göteborg, Sweden: birth to 18 years of age. *Acta Paediatr*. 2000;89:582-92.
  24. Wikland KA, Luo ZS, Niklasson A, Karlberg J. Swedish population-based longitudinal reference values from birth to 18 years of age for height, weight and head circumference. *Acta Paediatr*. 2002;91(7):739-54.
  25. Persson I, Ahlsson F, Ewald U, et al. Influence of perinatal factors on the onset of puberty in boys and girls: implications for interpretation of link with risk of long term diseases. *Am J Epidemiol*. 1999;150:747-55.
  26. Wasserman RM, Holmbeck GN, Lennon JM. A longitudinal assessment of early pubertal timing as a predictor of psychosocial changes in adolescent girls with and without spina bifida. *J Pediatr Psychol*. 2012;37:755-68.
  27. De Sanctis V, Soliman AT, Di Maio S, Soliman N, Elsedfy H. Long-term effects and significant adverse drug reactions (ADRs) associated with the use of gonadotropin-releasing hormone analogs (GnRHa) for central precocious puberty: a brief review of literature. *Acta Biomed*. 2019;90(3):345-59.
  28. Ergun-Longmire B, Vining-Maravolo P, Graham B, Greydanus DE. A narrative review: treatment outcomes of central precocious puberty. *Pediatric Med*. 2023;6:15.

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