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Prevalence of Beckwith Wiedemann Syndrome and Risk of Embryonal Tumors in Children Born with Omphalocele

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ABSTRACT

Aim of the study: Children with omphalocele have an increased prevalence of Beckwith Wiedemann syndrome (BWS) and thus a suspected increased risk of developing embryonal tumors, e.g. Wilms tumor, hepatoblastoma, neuroblastoma and rhabdomyosarcoma. The aim of this study was to examine the prevalence of BWS and the risk of embryonal tumors amongst patients born with omphalocele.
Methods: A population-based cohort was used, including all children born in Sweden 1/1 1997–31/12 2016. Patients with omphalocele were identified through the Swedish National Patient Register and the Swedish Medical Birth Register. For each case of omphalocele ten age and sex matched individuals unexposed for omphalocele were randomly selected for comparison. Data on BWS and embryonal tumors were collected from the Swedish National Patient Register and the Swedish National Cancer Register.
Main results: Out of 207 cases of omphalocele, 15 (7.2%) were diagnosed with BWS. None of the children with omphalocele had yet developed any kind of embryonal tumor (median follow-up time 8 years). None of the 2070 controls were diagnosed with BWS but 3 (0.1%) of them had developed embryonal tumors during a median follow-up time of 10 years.
Conclusions: In this study the prevalence of BWS amongst children born with omphalocele is in the lower range of previously reported figures. Also, the prevalence of embryonal tumors amongst children with BWS is lower than expected and the risk of embryonal tumors in children with omphalocele and BWS might not be as high as previously stated. This must be taken into consideration when counseling parents prenatally.
Type of Study: National register cohort study.
Level of Evidence: II.

1. Introduction

Children born with the rare abdominal wall defect omphalocele suffer from high morbidity, and to some extent also mortality. This is strongly connected to its association with other anomalies, chromosomal defects and syndromes [1–3]. Beckwith Wiedemann Syndrome (BWS) is a congenital overgrowth disorder and one of the most common syndromes amongst children born with omphalocele. Embryonal tumors such as Wilms tumor, neuroblastoma, hepatoblastoma or rhabdomyosarcoma are rare in the general population, but BWS entail an increased risk [4,5]. Therefore, children with BWS are monitored more closely during childhood with respect to tumors. An expert consensus [6] and the Swedish National Board of Health and Welfare recommend monitoring of children with BWS with ultrasound every three months during childhood.

BWS is not always evident at birth but prenatal suspicions, often due to macroglossia or macrosomia in combination with omphalocele, are in European settings raised in about 40% of cases with later confirmed diagnosis [7]. Diagnosis is firstly based on typical features of BWS defined in protocols [6,8] according to which

Abbreviations: BW, Birth weight; BWS, Beckwith Wiedemann syndrome; GW, Gestational week; IC2, Imprinting center 2; ICD, International Classification of Diseases; IQR, Interquartile range; n, Absolute value; NPR, National Patient Register; MBR, Medical Birth Register; TOP, Termination of pregnancy.

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cardinal features like omphalocele, macroglossia, lateralized overgrowth, hyperinsulinism and multifocal Wilms tumor give high probability of BWS. Additional features including macrosomia, facial nevus flammeus, ear creases or pits, transient hypoglycemia and embryonal tumors increase the probability. If suspicion is raised genetic testing should be performed and can, in up to 80% of cases, confirm the diagnosis [6,9] and provide more information on individual risk. Some patients with BWS will not be diagnosed until they develop an embryonal tumor and it's believed that many cases of BWS are undiagnosed.

Omphalocele is maybe the most important prenatal sonographic feature of BWS. Recent studies investigating the phenotype of known genetic alterations of chromosome 11p15, consistent with BWS, found that 11–66% of individuals with BWS were born with omphalocele [7]. Prenatal detection of BWS can be of outmost importance to prepare for a potentially difficult delivery due to large baby and possible premature birth. Hypoglycemia and possibly also feeding difficulties due to large tongue can, if not recognized, harm the newborn who otherwise do not usually have any cognitive impairment.

Over 50% of the parents expecting a child with omphalocele opt for termination of pregnancy (TOP) [1,3,10]. It is probable that associated anomalies and suspected BWS affect that decision. How common BWS is amongst children with omphalocele and if these children are at even higher risk of developing an embryonal tumor has not been extensively studied.

The aim of this study was to provide additional information about the risk of embryonal tumors in patients with omphalocele and BWS, which can be of value when counseling families with a prenatal diagnosis of omphalocele, and when designing patient-tailored follow-up programs for omphalocele and BWS.

2. Method

2.1. Study design

We performed a population-based cohort study with prospectively gathered data from registers held by Swedish National Board of Health and Welfare. Out of a national cohort, including all children born in Sweden between 1st of January 1997 and 31st of December 2016, all cases of omphalocele were identified. Omphalocele was defined as the International Classification of Diseases 10th revision (ICD-10) code Q79.2. To avoid inclusion of misclassified cases each subject had to satisfy one of the following inclusion criteria.

1. Omphalocele as main diagnosis and a surgical intervention code specific for omphalocele.
2. At least one admission, during the first 30 days of life, to a tertiary pediatric surgical center with an in hospital stay of a minimum of seven days and omphalocele as the main diagnosis.

For every case of omphalocele ten unexposed individuals, matched for sex and age, were randomly selected. Omphalocele was defined as exposure. BWS and embryonal tumor were both separate outcomes.

All included individuals with the ICD-10 code Q873, congenital malformation syndromes involving early overgrowth, were identified. Q873 is the diagnostic code that includes BWS and a few other extremely unusual diagnoses. If an individual has omphalocele, the additional Q873 diagnose implicates BWS as the diagnoses are rare but associated. Subsequently, the registers were searched for embryonal tumors within the exposed and unexposed cohorts. Embryonal tumor was defined as ICD-code C74.9 Neuroblastoma, C64 Wilms tumor, C22 Hepatoblastoma or C49 Rhabdomyosarcoma.

2.2. Data resources/registers

The Swedish National Patient Register (NPR) was established in the 1960's and covers all in-patient care, including diagnosis and surgical procedures, since 1987. NPR also covers specialist outpatient care since 2001 but not primary care. The underreporting of data is considered very low [11–13]. Data concerning diagnosis of omphalocele, BWS, associated malformations and embryonal tumors were collected from NPR.

Founded in 1973, the Medical Birth Register (MBR) covers 96–99% of all live and stillbirths with a gestational age of 22 weeks or more in Sweden [14]. The register holds prenatal, perinatal and postnatal data on both the mother and the newborn who can be linked by their personal identity numbers. Data on diagnoses and birth characteristics was gathered from MBR.

The Swedish Cancer register holds information on cancers in Sweden since 1958 and is held by the National Board of Health and Welfare. Health care providers are obliged to report all detected cancers, also if diagnosed at autopsy. About 60,000 malignant cancers are reported every year but only a fraction of those constitute childhood cancer. The completeness of the register is considered high, around 96% [15] and assumingly higher when focused on the pediatric cancer coverage. From the Swedish Cancer register data on embryonal tumors were collected.

The Swedish Causes of Death Register exists since 1961 and is held by the National Board of Health and Welfare. All deaths in Sweden and deaths of Swedish citizens abroad are registered. The cause of death is specified by the treating physician or by pathologist performing postmortem studies. Data on causes of deaths within the cohort were collected from Causes of Death Register.

The Swedish Population Register is held by Statistics Sweden and covers all Swedish citizens and individuals living in Sweden for longer than a year. The unexposed cohort, matched for age and sex, were randomly selected from this register. Again, the individual's personal identity numbers were used to link between the Swedish Population Register and the medical registers held by the National Board of Health and Welfare. The Swedish Population register was used when randomly selecting the unexposed cohort.

The personal identity number, a ten-digit unique personal identity code assigned to each Swedish resident at birth, was used for correct linkages between the registers used. The data extractions from all the above mentioned registers were made in 2018.

2.3. Variables

Exposure was omphalocele. Outcome was BWS diagnosis and the *prevalence* of BWS was registered for both the children born with omphalocele, i.e. exposed cohort, and those without omphalocele, the unexposed cohort. The second outcome was embryonal tumor and the *incidence* of embryonal tumor among exposed was compared to the incidence among the unexposed.

Survival was calculated based on the numbers of living study persons at follow up divided by the number of live born in the exposed cohort as well as the unexposed cohort.

Patient characteristics such as *sex, birth weight*, *gestational age at birth*, *delivery mode* and *associated anomalies, age at tumor diagnosis* and *median follow up time* were explored in exposed and unexposed.

2.4. Statistical analysis

Categorical data is presented as absolute value (n) and frequency (%) and continuous data as mean or median with interquartile range (IQR).

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Statistical tests used were Fisher's Exact test for categorical variables and Wilcoxon sum-rank test for numerical variables. The missing data on mode of delivery was excluded for the tests. Significance was defined as $p \leq 0.05$ and data analyses were preformed using R software version 2.38 [16].

3. Results

During the study period 2,082,672 children were born in Sweden. Of those 207 individuals were born with omphalocele and constitute our exposed cohort. Among the children born with omphalocele, 15 individuals (7.2%) also had a diagnosis of BWS. The unexposed cohort consisted of 2070 individuals. No one in the control group had a BWS diagnosis, se Fig. 1.

The cohorts were slightly but not significantly male dominated. The exposed cohort had lower birth weight than the unexposed and was more often born premature with median of 37 versus 39 gestational weeks (GW). Children born with omphalocele and associated BWS had a lower median GW, 34, but higher birth weight than the rest of the exposed group. The children with BWS were more often delivered with acute caesarean section compared to both the unexposed and the rest of the exposed group. Table 1 shows patient characteristics for both exposed and unexposed individuals, as well as for the sub-group of patients with BWS diagnosis.

The children exposed to omphalocele had a significantly greater prevalence of associated malformations then the unexposed cohort (Table 1). This was true also for the children with omphalocele and BWS, but they had no cases of chromosomal abnormality. The most common associated malformations were heart defects both for the children diagnosed with BWS and for the total omphalocele cohort.

None of the children with omphalocele, and hence none of the children with BWS, developed an embryonal tumor during childhood. In the unexposed group one child was diagnosed with Wilms tumor, one with rhabdomyosarcoma and one with hepatoblastoma (Table 2).

The median follow up time was eight years for the cohort exposed to omphalocele and ten years for the unexposed cohort. The difference in follow up time is due to the higher survival in the unexposed cohort. There was an increase of BWS diagnosis towards the end of our study period, which affects the follow up time for exposed individuals with BWS, see Table 1.

4. Discussion

4.1. Key results

In this national cohort of 207 individuals with omphalocele the prevalence of BWS is in the lower range of previously reported figures. No embryonal tumors were detected in the cohort exposed for omphalocele during the study period whilst three were detected in the unexposed cohort. The risk of embryonal tumors in children with omphalocele and BWS might not be as high as previously stated. This must be taken into consideration when counseling parents prenatally and may add to knowledge used for designing follow-up programs.

Previous studies [6] have indicated that BWS is more often present in children with omphalocele and some specific malformations but normal karyotype. In accordance with this our group of children with BWS had less frequency of altered karyotype then the rest of the omphalocele cohort. However, they did have an increased frequency of associated malformations compared to the unexposed cohort.

Children with both omphalocele and BWS were born premature to a larger extent, however the birth weight was higher than in children born with omphalocele without associated BWS. High rate of premature birth amongst children born with BWS have been previously documented [7]. Although vaginal birth has proven to be an option with congenital abdominal wall defects [17] the majority is still delivered with caesarean section and often one or two weeks before term for both medical and logistical reasons. In line with this, the exposed group had a higher rate of caesarean section then the unexposed. However, the slight preterm elective caesarean section cannot explain the lower median gestational week of the children with BWS since they were born with acute caesarean to a higher extent than the unexposed cohort but also compared to rest of the exposed cohort. This suggests complicated deliveries and

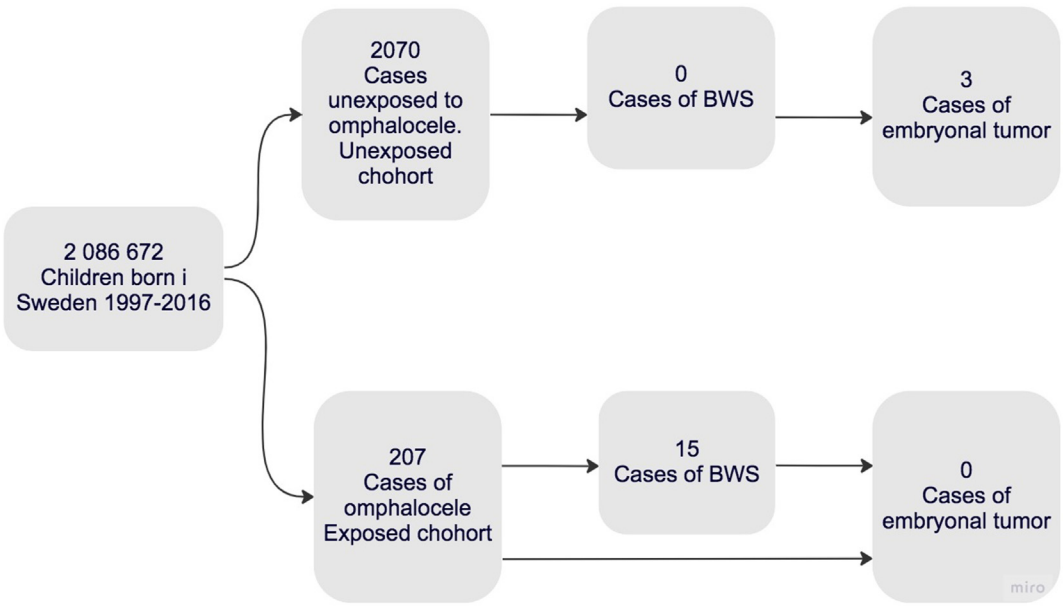

Fig. 1. Flowchart showing the recruitment of population-based cohorts and main results. Note that the recruitment was population based, the individuals with Beckwith Wiedemann were all found in the cohort exposed to omphalocele but the embryonal tumors were all found in the unexposed cohort.

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Table 1
Baseline characteristics. Table showing baseline characteristics and outcome for the exposed and unexposed study cohorts.

	Exposed		P[1]	Unexposed	P[2]
	Omphalocele without BWS	Omphalocele + BWS			
n.	192	15		2070	
Sex, n. female (%)	79 (41)	8 (53)	0.420	870 (42)	0.436
BW, median [IQR]	2890 [2339–3294]	3305 [2923–3950]	0.069	3535 [3200–3897]	0.196
BWS, n. (%)	15 (7.2)	15 (100)		0	
GW, median [IQR]	37 [36–39]	35 [34–37]	0.020	40 [38–40]	<0.001
Mode of delivery, n. (%)					
Vaginal birth	60 (31)	5 (33)	0.008	1428 (69)	<0.001
Elective caesarean section	67 (35)	1 (7)		145 (7)	
Acute caesarean section	33 (17)	7 (47)		191 (9)	
Missing data	32 (17)	2 (13)		306 (15)	
Associated malformations, n. (%)	121 (63.0)	8 (53.3)	0.581	194 (9.4)	<0.001
Chromosomal, n. (%)	23 (12)	0 (0)		7 (0.3)	
Median age at follow up in years [IQR]	8 [2–15]	5 [3–10]	0.525	10 [4–15]	0.058
Embryonal tumors, n. (%)	0 (0)	0 (0)		3 (0.1)	1.000
Survival, n. (%)	163 (84.9)	15 (100)	0.227	2066 (99.8)	1.000

P[1]: Comparing potential differences within the exposed group, between the children with and without BWS.
P[2]: Comparing potential differences between the BWS cohort and the unexposed cohort.
Abbreviations: Birth weight (BW), Beckwith Wiedemann syndrome (BWS), gestational week (GW), Interquartile range (IQR).

confirms the importance of raising prenatal suspicions of BWS when implied.

4.2. Interpretation and generalizability

The prevalence of BWS among children born with omphalocele is in the lower range of what has previously been reported [18,19]. This might indicate that we fail to identify and diagnose or, possibly, that fetuses with omphalocele and BWS are more likely to be aborted than fetuses with omphalocele but without BWS. If the latter is the case this study can provide important information to expectant parents since the incidence of embryonal tumor among the children with BWS also is less than expected. We anticipated at least a few cases of tumor in the exposed cohort but instead the prevalence in the unexposed cohort was surprisingly high. Omphalocele is not believed to be protective but it can be speculated as to whether children with BWS and omphalocele more often have a beneficial mutation than those with BWS without omphalocele.

Although human genes come in doublets with one copy from each parent, a few of them should only have one active copy while the other gene is inactivated by methylation. This selective expression or inactivation of genes depending on which parent it was inherited from is called genomic imprinting. BWS is an imprinting disorder causing dysregulation of growth [20] but with variable expressivity. Most often altered methylation of chromosome 11p15 is the root and a few different genetic causes have been detected. The altered methylation affects the expression of genes that control growth such as IGF2/H19 and KCNQ1/CDKN1C. The different alterations of chromosome 11p15 causing BWS result in different predisposition to the development of tumors [4] and some causes carry higher risk of certain tumors than others. Previous studies of children born with BWS show a 7.4–15% risk of developing an embryonal tumor during childhood [5,21,22] but as for the most common cause of BWS, hypomethylation of imprinting center 2 (IC2), the risk is lesser with about 2.5% tumor prevalence [4]. Mussa et al. showed in a comprehensive review that omphalocele is strongly associated to hypomethylation of IC2 and to CDKN1C mutations, being present in 50–70% of those cases [23]. Even if omphalocele is not protective, the combination of BWS and omphalocele means that chances are good of the more favorable hypomethylation of IC2 as the cause of BWS. This is in line with our results. Even though certain subtypes have higher predisposition to certain types of cancer, it is still difficult to recommend applying different protocols to different BWS patients [6,21].

Table 2
Cases of embryonal tumor. Table showing the three cases of embryonal tumor within the study. Note that none of the individuals with tumor diagnosis were exposed to omphalocele neither to BWS.

Tumor diagnosis	n.	Status	BWS	Age in years at tumor diagnosis	Survival
Rhabdomyosarcoma	1	unexposed	No	0.2	Yes
Hepatoblastoma	1	unexposed	No	3.6	No
Wilms tumor	1	unexposed	No	5.0	Yes

4.3. Strength and limitations

The strength of this study is its nationwide coverage. Neither omphalocele nor malignant tumors amongst children are missed in Swedish healthcare. The registers provide good coverage and make it possible to perform population-based studies like this one. Even though the registers are comprehensive, BWS can possibly or even likely be under diagnosed. Furthermore, we will never be able to appoint the actual incidence of omphalocele and BWS since causes and figures of TOP are precarious.

A larger study population would have been beneficial to increase the accuracy of the study but longer follow up time would most likely not change any results since the risk of developing embryonal tumors that BWS entail is most increased in the first decade of life, with the highest incidence during the first 2 years of life [6]. However, to lengthen the study period would be more interesting, both to gain larger material but also since the BWS diagnoses had a tendency of becoming more common towards the end of the period studied. If this is a true increase one can only speculate on if the diagnose has become more recognized or actually more common. Lastly, a future complementary study on our BWS cohort with both gene testing and case record reviews would be both interesting and feasible.

5. Conclusion

Seven percent of children with Omphalocele had BWS during our study period in Sweden. Those children have a risk of morbidity but very good survival and a lesser risk of embryonal tumors then apprehended.

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Declaration of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. The study was approved by the Regional Ethics Review Board in Stockholm. Dir. 2016/2265-31/1.

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