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Epidemiology of Dandy-Walker malformation in Europe: a EUROCAT population-based registry study

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ABSTRACT

Background. Dandy Walker (DW) malformation is a rare and severe congenital anomaly of the posterior fossa affecting the development of the cerebellum and the fourth ventricle. **Objective**. The aim of this study was to investigate the epidemiology of DW malformation, using data from the European population-based registries of congenital anomalies in the EUROCAT network. **Methods.** Anonymous individual data on cases of DW malformation diagnosed in 2002-2015 from 28 registries in 17 countries were included. Prevalence, prenatal detection rate, proportions and types of associated anomalies were estimated. Cases of DW variant were considered and analysed separately. **Results.** Out of 8,028,454 surveyed births we identified a total of 734 cases, including 562 DW malformation cases and 172 DW variant cases. The overall prevalence of DW malformation was 6.79 per 100,000 births (95%CI: 5.79-7.96) with 39.2% livebirths, 4.3% fetal deaths from 20 weeks gestational age, and 56.5% terminations of pregnancy after prenatal diagnosis of fetal anomaly at any gestation (TOPFA). The livebirth prevalence was 2.74 per 100,000 births (95%CI: 2.08-3.61). The prenatal detection rate was 87.6%. Two-hundred and seventy-three cases (48.6%) had an isolated cerebral anomaly and 24.2%, 19.2%, and 5.5% cases were associated with other structural non-cerebral anomalies, chromosomal anomalies and genetic syndromes, respectively. The prevalence of DW variant was 2.08 per 100,000 (95%CI 1.39-3.13). **Conclusions.** This European population-based study provides the epidemiological profile of DW malformation. All birth outcomes were analysed and TOPFA represented more than half of the cases. About 50% of the cases of DW malformation were associated with other non-cerebral anomalies. Large populations and all birth outcomes are essential in epidemiological studies of rare and severe congenital anomalies.

BACKGROUND

Dandy Walker (DW) malformation is a rare congenital anomaly of the brain. It is the most common anomaly of the posterior fossa affecting the development of the cerebellum and the fourth ventricle. DW malformation is diagnosed when the following three main signs are identified: agenesis or hypoplasia of the cerebellar vermis, cystic dilatation of the fourth ventricle, and an enlargement of the posterior fossa [1-3]. Hydrocephalus is present in about 80% of the cases and it is considered a consequence and not a specific part of the anomaly [2, 4-6]. A subset of DW malformation is often reported and frequently classified with the term of DW variant [3]. DW variant is in general a less severe form of DW malformation, in particular the enlargement of the posterior fossa is not present [1]. However, some authors recommend not to use the term “Dandy Walker variant” due to the lack of specificity and a more specific description is suggested [2,4]. DW malformation can be considered a part of a spectrum called DW complex, which also includes DW variant and mega cisterna magna [7]. Cases of mega cisterna magna were not included in the present

study**.** Signs and symptoms of DW malformation, mainly related to hydrocephalus and cerebellar and cranial nerves dysfunctions, are generally present during the first year after birth [5]. Nowadays, improved diagnostic techniques enable earlier diagnosis of DW malformation and the proportion of cases with a prenatal diagnosis is increasing [2]. Prevalence estimates of about 1:25,000 – 1:30,000 reported in the literature are based on case-series studies [8] which include only live birth (LB) cases. One population-based study in the UK which included 47 cases of DW malformation and DW variant, reported an overall prevalence of 8.5 per 100,000 births [9]. A study based on about 45,000 LBs in the only hospital of an area of Saudi Arabia reported a prevalence of 1 per 100,000 births [10]. ORPHANET, the European portal for rare diseases and orphan drugs, reports a birth prevalence estimate for isolated DW malformation of 1 per 100,000 births [11]. Association with other congenital anomalies of the nervous system and other organ systems (e.g. cardiovascular, genitourinary, musculoskeletal, gastrointestinal, oro-facial, etc.) has been reported [6,8,12-15]. The neonatal and infant mortality are estimated as 14% and 25%, respectively [16]. DW malformation may be associated with poor intellectual outcome particularly when other cerebral anomalies are present [17-19]. DW malformation has been reported to have an heterogeneous aetiology, including mutations in genes of fibroblast growth factors and in genes in the sonic hedgehog (Shh) signalling pathway [20-22]. Many studies report associations with chromosomal anomalies and genetic syndromes [4,14,23,24].

As most of the studies on DW malformation available are based on case-series or case reports with liveborn infants, there is a need for population-based studies covering all birth outcomes [3]. The aim of this study was to describe the epidemiology of DW malformation using population-based data from 28 EUROCAT registries of congenital anomalies. Cases of DW variant were also included in the study and analysed separately.

METHODS

We analysed cases of DW malformation collected by the European population-based registries of congenital anomalies belonging to the EUROCAT network. EUROCAT- European Surveillance of Congenital Anomalies - is the European network of the registries of congenital anomalies, which collects cases diagnosed mostly to up to 1 year of age. All registries report cases annually to the central database operated at the European Commission's Joint Research Center (JRC) in Italy [25,26]. EUROCAT includes all birth outcomes: LBs, late fetal deaths (>=20 weeks gestation) and terminations of pregnancy for fetal anomaly following prenatal diagnosis at any gestation (TOPFA) [25,27]. The registries collect data on structural anomalies, monogenic and teratogenic syndromes, and chromosomal anomalies. Minor anomalies are excluded according to the EUROCAT guidelines [28]. All cases are coded by using the International Classification of Diseases, Tenth Revision (ICD-10) with British Paediatric Association (BPA)

one-digit extension. For each case, all major anomalies are coded according to the EUROCAT guidelines [28]. All EUROCAT full member registries [29] were invited to participate in the study. Cases of DW malformation and DW variant born between 1 January 2002 and 31 December 2015 and notified to the 28 registries in 17 different countries that agreed to participate, formed the study population. Anonymous individual data on DW cases were extracted from the JRC-EUROCAT central database using the ICD10-BPA code Q031, and a search through the text descriptions. Variables used for this study were: year of birth, birth outcome (LB, late fetal deaths, TOPFA), timing of diagnosis (prenatal or postnatal), one-week survival and maternal age. All extracted cases were confirmed by the local registry and distinguished as a case of DW malformation or a case of DW variant. As denominators we used the number of total births to mothers resident in the area covered by each registry stratified by year and maternal age. Following the EUROCAT multiple flowchart classification, cases of DW were classified into isolated cerebral anomaly, multiple congenital anomalies, associated with chromosomal anomalies, associated with genetic syndromes, isolated neural tube defect and teratogenic syndrome [28,30]. Two clinicians (IB and EG) reviewed all the cases to confirm the classification. Cases of DW associated only with cerebral anomalies were defined in the text as isolated. We calculated prevalence, prenatal detection rate, birth outcomes, and proportions of associated anomalies. The analyses were performed separately for the cases of DW malformation and DW variant in order to detect possible differences among the two forms. Overall and LB prevalence were estimated using Poisson regression with random effects models in order to account for potential heterogeneity across registries. Ninety-five percent confidence interval (95%CI) for prevalence estimates were calculated. Time trend prevalence was tested by using models based on a Poisson distribution. The χ^2 test for homogeneity was performed to test differences in prevalence estimates across registries. Results with a p value <0.05 were defined as statistically significant. Statistical analyses were performed using STATA version 13.0 (StataCorp LP, College Station, TX, USA).

RESULTS

In the study period (2002-2015) 8,028,454 total births were surveyed. We identified a total of 734 cases, of which 562 (76.6%) were diagnosed with DW malformation and 172 (23.4%) with DW variant. The prevalence of DW malformation was 6.79 per 100,000 births (95%CI: 5.79-7.96) (Table 1). The LB prevalence was 2.74 per 100,000 (95%CI: 2.08-3.61). Over the two time-periods 2002-2008 and 2009-2015, the prevalence increased slightly, but the difference was not statistically significant. The prevalence of DW variant was 2.08 per 100,000 (95%CI: 1.39-3.13) and was stable over the two time-periods. The overall prevalence of DW malformation and DW variant was 8.85 per 100,000 (95%CI: 7.43-10.54).

DW malformation

There were major differences in prevalence among regions and countries (p<0.001) with the highest prevalence of DW malformation observed for the registries of Wales (14.12 per 100,000) and OMNI-Net in Ukraine (11.40 per 100,000) (Figure 1). The most frequent birth outcome for DW malformation was TOPFA with 317 cases (56.5% of total cases) (Table 2). There were 220 liveborn cases (39.2%) and 24 fetal deaths (4.3%). The proportion of TOPFA after a prenatal diagnosis decreased significantly over the two time-periods (73.1% vs 62.2%; p=0.01). The majority of cases were classified as isolated (n = 273, 48.6%), 24.3% were classified as multiple congenital anomaly, 19.2% had an associated chromosomal anomaly and 5.5% were diagnosed with a genetic syndrome. The prevalence of isolated DW malformation was 3.41 per 100,000 (95%CI: 2.91-4.80). The proportion of TOPFA was not significantly different between isolated and multiple cases, but was significantly higher (p<0.001) in chromosomal cases than in both isolated and multiple cases.

The overall prenatal detection rate was 87.6% (Table 3) and no difference was observed among isolated and multiple cases. There was no significant difference in the prenatal detection rate in the two time periods (84.9% vs 89.7%). In seven registries in six different countries all the cases were diagnosed prenatally. The median gestational age at prenatal diagnosis was 20 weeks (range 10-38) with a high variability among registries. It remained constant over time and did not differ among isolated, multiple and chromosomal cases. The male-to-female ratio was 1.11 and the difference was not statistically significant. The mean maternal age was 29.8 (standard deviation 5.9) years. Prevalence of non-chromosomal cases did not increase with the increase of maternal age. About eleven percent of the total cases of DW malformation was associated with a congenital heart defect, 5.9% with an anomaly of the urinary system and 4.6% with an anomaly of the limbs (Table 4). The most frequent structural anomalies were: ventricular septal defect, cleft lip with or without cleft palate, atrial septal defect, hypospadias and polydactyly. It is noteworthy that we observed five cases associated with the rare anomaly “congenital malformations of intestinal fixation”. Among the anomalies of the nervous system, we observed 58 cases of congenital anomalies of the corpus callosum (10.3%). Other anomalies of nervous system were reported, such as: microcephaly, holoprosencephaly, ventriculomegaly and occipital encephalocele. The most common chromosomal anomalies were Patau’s syndrome and Edward’s syndrome (4.1% and 3.6%, respectively). Among the 108 cases with a chromosomal anomaly, 22 (20.4%) had cerebral anomalies only. Among the 31 cases associated with genetic syndromes, 10 had a diagnosis of Meckel-Gruber syndrome.

DW variant

Birth outcomes for DW variant were 79 LBs (45.9%), 81 TOPFA (47.1%) and 12 fetal deaths (7.0%) (Table 2). Among the cases of DW variant 43.6% were isolated, 25.0% were multiple congenital anomaly, 23.8% were diagnosed with a chromosomal anomaly, and 3.5% with a genetic syndrome. The prenatal detection rate was 83.0% with no difference between the two time periods. No significant gender difference was

observed (male-to-female ratio = 1.13). About thirteen percent of the total cases of DW variant were associated with a congenital heart defect, 5.8% with an anomaly of the urinary system and 5.2% with a limb anomaly (Table 5). Eighteen cases (10.5%) with congenital anomalies of the corpus callosum were observed. Among the 41 cases with a chromosomal anomaly, 18 (43.9%) had a diagnosis of Patau's Syndrome.

Comparing DW malformation and DW variant, the proportion of TOPFA in DW malformation was significantly higher than in DW variant for all cases (56.5% vs 47.1%; p=0.03) and for isolated cases (55.1% vs. 41.3%; p= 0.03). The profile of the associated anomalies of DW variant was very similar to DW malformation. We observed a significantly higher proportion of Patau's syndrome in DW variant (10.5%) than in DW malformation (4.1%) and a higher proportion of oro-facial clefts in DW malformation (3.4% vs 1.2%); this difference was not statistically significant. Survival at one week for LBs with DW malformation and DW variant were almost the same (90.8% and 93.2%, respectively). No significant difference was observed among isolated, multiple and chromosomal cases.

DISCUSSION

This population-based study analysed a large series of DW malformation cases in Europe including all birth outcomes: LBs, TOPFA and late fetal deaths. We observed a total prevalence of DW malformation of 6.79 per 100,000. This is higher than prevalence estimates from other studies [8,10], most of which were based on case series and mainly focused on LB cases. Indeed, the contribution of TOPFA cases is relevant as this is more than half of all cases in this study, confirming that for studies of the prevalence of major and severe congenital anomalies all birth outcomes should be included. Major difference in the prevalence among registries was observed. Geographical difference in prevalence may be difficult to evaluate for a rare anomaly as DW. Changes in case ascertainment methods and/or in prenatal and postnatal diagnostic methods may be contributing factors [31]. The prevalence of DW variant observed in our study was 2.08 per 100,000 births. The proportion of TOPFA in cases of DW malformation was significantly higher than in cases of DW variant and this result is consistent with findings by Ecker et al., 2000 [12]. About half of the cases of DW malformation were classified as isolated cerebral anomalies. About 10% of the cases were associated with congenital malformations of corpus callosum which is consistent with other studies [12,13]. We observed in particular, associations with anomalies of the heart, oro-facial clefts, limb, gastrointestinal, and genito-urinary system. These associations have been reported in other studies although with different proportions [6,8,12-15,32], however these studies were based on case series and mainly on LB cases. We observed that more than 20% of cases were associated with chromosomal anomalies, which is in agreement with other studies [15,23]. The most frequent chromosomal anomalies were trisomy 18

(Edward's syndrome) and trisomy 13 (Patau's Syndrome) which was in accordance with other studies [14,15]. The observed association with genetic syndromes such as Meckel-Gruber was already noted [4]. Diagnosing a genetic syndrome in cases of DW is important as most of them, including Meckel-Gruber, are autosomal recessive and therefore have a high recurrence risk in subsequent pregnancies. The profile of the associated anomalies observed in DW variant was similar to that observed for DW malformation. This result has been reported in two studies which investigated the associations separately in the two forms of DW [12,13]. We observed a higher association with Patau's syndrome in cases with DW variant and a higher association, although not statistically significant, with oro-facial clefts in DW malformation. In our study, we found that half of all cases were associated with other anomalies, chromosomal anomalies or genetic syndromes. It is important to identify the presence of other anomalies after a prenatal or postnatal diagnosis of DW, as the association with other anomalies may have a major impact for the prognosis and in the case of prenatal diagnosis may affect the parents' decisions about whether to continue with the pregnancy. A study of survival found that the risk of mortality is higher in infants with multiple anomalies than in isolated cases [16]. In general, prognosis is recognised to be worse when associated anomalies are present [4-6,19]. Prenatal diagnosis may have an influence on the prenatal and postnatal management [4]. Most cases of DW malformation are diagnosed prenatally [5,33]. The prenatal detection rate in this European population was high and about 90% of the cases had a prenatal diagnosis in the period 2009-2015. This is likely to be due to the widespread prenatal ultrasound screening that is now offered to all pregnant women in most European countries and/or an increased use of prenatal MRI scans for diagnostic confirmation [34]. Among the prenatally diagnosed cases the proportion of TOPFA decreased over the study period. A possible explanation of this decrease may be an improvement of the overall management of affected patients, in terms of outcome and prognosis [5], which may have influenced the parents' decision to continue with the pregnancy or not. Prenatal imaging can detect anomalies of the posterior fossa and the complete development of cerebellar vermis at about 18 weeks of gestation, thus 18-20 weeks of gestation is indicated as good timing for prenatal ultrasound screening [2,12]. In our study, we found a median gestational age at diagnosis of 20 weeks which remained constant over time. It is a limitation in the EUROCAT data, that gestational age at diagnosis is recorded only for the first anomaly diagnosed. For cases with multiple congenital anomalies, the first diagnosis may not be Dandy-Walker. However, in our study, gestational age at diagnosis did not differ among isolated, multiple and chromosomal cases. The ICD10 code used for DW is Q031. This code is reported within the subchapter of congenital hydrocephalus in the ICD10 classification (code Q03) even if for some cases hydrocephalus is not present. Compared to the prevalence of congenital hydrocephalus reported by the EUROCAT [35], the total prevalence of DW malformation and DW variant detected in our study represents about 17% of the total cases belonging to the group of hydrocephalus. Assuming that 80% of the cases of DW have hydrocephalus, we estimated that about 4% of the cases of congenital hydrocephalus are wrongly classified as hydrocephalus by the ICD10. As

cases of DW without hydrocephalus should be excluded in the epidemiological study of hydrocephalus [36], the definition of a more accurate ICD coding of DW malformation is recommended. Furthermore, the Q031 code is reported also for Atresia of foramina of Magendie and Luschka that were initially believed to always be associated with DW malformation, but in some cases it is found in infants without DW malformation [5,37]. Thus, a better definition of the classification of DW malformation is needed. The main strength of this multi-centre population-based study is the large series of DW malformation cases including all birth outcomes. The use of data from 28 registries increased the power of the study, which is a critical point when a rare disease is investigated, and allowed us to compare outcomes between classification groups. Furthermore, data were collected by population-based registries of congenital anomalies and not from clinical/hospital centres. Thus, all the residing population was surveyed and selection bias has been limited [31]. In addition, in our study we distinguished cases of DW malformation from cases of DW variant. A limitation of our study is a possible under-reporting by those registries which are not able to collect cases diagnosed after the neonatal period, or follow–up of a suspected diagnosis at birth. However, in our study we observed that most of the cases of DW malformation are prenatally diagnosed.

CONCLUSIONS

To our knowledge this is the largest population-based study of DW malformation performed in Europe. The study considered all birth outcomes including TOPFA, which represent about half of the total cases. The overall prevalence of DW malformation and DW variant were 6.79 and 2.08 per 100,000, respectively. The livebirth prevalence of DW malformation was 2.74 per 100,000 births. About 90% of the cases were diagnosed prenatally and only 50% were isolated cerebral anomalies. This is important since the presence of other anomalies, such as Meckel Gruber syndrome or severe chromosomal anomalies, is related to a poor prognosis. As the aetiology is largely unknown for isolated and multiple cases, further studies are needed to better understand and possibly prevent these major cerebral anomalies.

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