

The Validation of Neural Tube Defects in the General Practice Research Database

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ABSTRACT

Background: The General Practice Research Database (GPRD) has been used to identify associations between pregnancy medication exposures and birth defects, but some experts have argued that databases cannot provide sufficiently detailed information for the valid identification of complicated congenital anomalies.

Objectives: Our objective is to determine if the GPRD's electronic medical records can be used to accurately identify cases of neural tube defects (NTD).

Methods: We identified and validated cases of NTDs within the GPRD. We created electronic case definitions of anencephaly, encephalocele, meningocele, and spina bifida and used these definitions to identify potential cases. We identified 217 potential NTDs in either a child's record or a mother's record. We attempted to validate these cases by querying the general practitioners using a short assessment form. For the NTD cases identified in the mother's record, we asked if the diagnosis was the mother's own or that of her fetus or offspring. We also requested details on what source of information the physician used to confirm the diagnosis and if any diagnostic tests were performed to confirm the diagnosis.

Results: Of 217 identified cases, responses to questionnaires were returned for 165 cases (76%). Of these cases, we were able to confirm an NTD diagnosis 71% (n = 117) of the time. In 14 cases, the algorithm incorrectly identified either the type of NTD or the date on which the NTD was first diagnosed, giving our identification algorithm an overall positive predictive value (PPV) of 0.62. The PPV varied depending on the NTD. The PPV for our algorithm was 0.81 for anencephaly, 0.83 for cephalocele, 0.64 for meningocele, and 0.47 for spina bifida. For 32% (n = 52) of our returned questionnaires, the only source reviewed to confirm the diagnosis was the electronic medical records.

Conclusions: Our identification algorithm was useful in identifying three of the four types of NTDs studied. Additional information is necessary to accurately identify cases of spina bifida.

CONFLICT OF INTEREST

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BACKGROUND

Neural tube defects (NTDs) are a group of severe central nervous system birth defects that occur when the neural tube fails to close during early embryonic development. NTDs are generally defined by the area of central nervous system that they affect. Anencephaly is the absence of brain material, encephalocele is an opening in the skull, and spina bifida and meningocele are openings along the spinal cord. While the birth prevalence of NTDs in the United Kingdom (UK) and Ireland has declined from 45 per 10,000 live and stillbirths in 1980 to 10 to 15 per 10,000 live and stillbirths in the 1990s through 2000, NTDs remain a common congenital anomaly.¹ The purpose of this study is to determine if the General Practice Research Database (GPRD) can be used to accurately identify NTDs.

METHODS

Data Source

The GPRD is a large anonymized, longitudinal database of patients' electronic medical records. The GPRD provides clinical information based on general practitioner records. The GPRD data contain approximately 46 million patient-years of follow-up, representing 10.1 million unique patients.² Over 460 general practices in the UK are currently submitting data to the GPRD on 3.2 million patients, or approximately 5% of the UK population.^{2,3}

Identification and Validation of Neural Tube Defect Cases

We identified new cases of anencephaly, encephalocele, meningocele, and spina bifida occurring between January 1, 1987 and September 14, 2004. The complete medical record profile for any individual with at least one NTD Read or Oxford Medical Information System (OXMIS) code in the data set was analyzed. Depending upon whether the NTD was found in a mother's or a child's record, the following exclusions were used.

Exclusions Among Mothers

- Any NTD records not within 210 days of a record indicating the woman was pregnant;
- Records dated January 1st of a given year (a convention used by general practitioners for recording historical information when the date was unknown) if not within 30 days of a pregnancy record;
- NTD records up to 60 days after the index diagnosis; and
- When two types of NTDs were recorded (e.g., a record for both meningocele and spina bifida was present), the second record was excluded.

Exclusions Among Children

- NTD records beyond 365 days from the estimated date of birth (the 15th of their birth month);
- All NTD records after the first NTD record; and
- All NTD records dated January 1st of a given year, if not within 30 days of the child's estimated birth date.

For each NTD identified, a questionnaire was sent to the general practitioner requesting a response to the following questions:

- Can you confirm the primary diagnosis found in the patient's record on this date?
 - Yes
 - No The actual NTD diagnosis is _____.
 - No Date of new NTD diagnosis _____.
 - No No actual NTD occurred.
- Is the diagnosis mentioned in Question 1 regarding the mother's own condition or is it a diagnosis for a mother's fetus or offspring? (ONLY CASES IN MOTHERS' RECORDS)
 - Mother's own condition
 - Diagnosis for mother's fetus or offspring
- What source was reviewed to answer Question 1? (Please check all that apply.)
 - Electronic medical record
 - Letter from specialist/consultant(s)
 - Paper chart or notes
 - Other _____ (Please specify.)
- If a neural tube defect was present, what type of examination/test was performed to determine the diagnosis for this patient? (Please check all that apply.)
 - Physical examination by you
 - Maternal serum α -fetoprotein
 - Amniocentesis
 - Amniotic fluid α -fetoprotein
 - Acetylcholinesterase (AChE)
 - Prenatal ultrasound examination
 - MRI
 - Other _____ (Please specify.)
 - Physical examination by another general practitioner
 - Physical examination by a neurologist
 - Physical examination by a pediatrician/obstetrician
 - Unknown
 - None

RESULTS

Figure 1. Progression of Records for Validated Neural Tube Defects in the General Practice Research Database Between 1987 and 2004

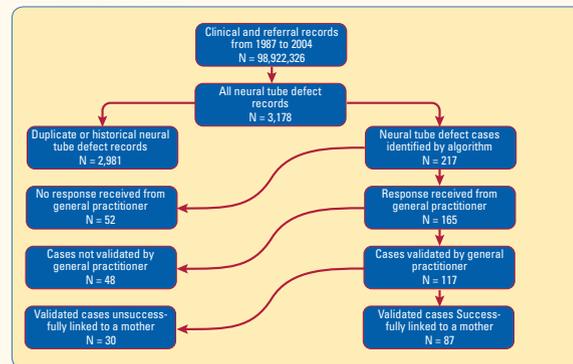


Table 1. Number of Neural Tube Defects Identified and Validated in the General Practice Research Database

Neural Tube Defect Type	Number of Electronically Identified Cases n	Returned Questionnaires n (%)	Validated Cases n (%)
Overall	217	165 (76)	117 (71)
Anencephaly	72	62 (86)	57 (92)
Cephalocele	10	6 (60)	5 (83)
Meningocele	20	14 (70)	11 (79)
Spina bifida	115	83 (72)	44 (53)

- Questionnaire return rates differed across NTD diagnoses (MH₂ = 4.1, df = 1, P = 0.04), with anencephaly having the highest overall response rate (86%) and cephalocele having the lowest overall response rate (60%).
- More responses were received for NTDs found in mothers' records (82%, 95% confidence interval [CI]: 76%-88%) than in children's records (64%, 95% CI: 52%-75%).
- Validation of the NTD did not vary by:
 - Presence in mother's record (69%, 95% CI: 60%-78%) or child's record (75%, 95% CI: 60%-87%);
 - Frequency of repeated codes in profile (MH₂ = 0.49, df = 1, P = 0.48).

Table 2. Positive Predictive Value of Identification Algorithm for Neural Tube Defects in the General Practice Research Database

Neural Tube Defect Type	Positive Predictive Value	95% CI
Overall	0.71	0.63-0.78
Anencephaly	0.81	0.69-0.90
Cephalocele	0.83	0.36-0.99
Meningocele	0.64	0.35-0.87
Spina bifida	0.47	0.36-0.60

- If we exclude spina bifida codes associated with spina bifida occulta (OXMIS/Read Codes: PG17.00 and 7419CO), the overall positive predictive value increases to 0.78, with only 5% of validated NTDs lost.

Table 3. General Practitioner Reported Diagnostics and Screening Tests Used in Neural Tube Defect Diagnosis in the General Practice Research Database*

	Ultrasound n (%)	Physical exam by Pediatrician/Obstetrician n (%)	AFP, MRI or Amniocentesis n (%)	Other Physical Exam n (%)	Other n (%)	None n (%)	Unknown n (%)	Total n (%)
Returned questionnaires	66 (40)	32 (19)	24 (15)	11 (7)	35 (21)	1 (1)	17 (10)	165
Anencephaly	42 (68)	9 (15)	8 (13)	0 (0)	16 (26)	0 (0)	3 (5)	62
Cephalocele	1 (17)	1 (17)	1 (17)	0 (0)	1 (17)	0 (0)	2 (33)	6
Meningocele	2 (14)	4 (29)	4 (29)	5 (36)	1 (7)	0 (0)	2 (14)	14
Spina bifida	21 (25)	18 (22)	11 (13)	6 (7)	17 (20)	1 (1)	10 (12)	83
Validated cases	61 (52)	27 (23)	24 (21)	10 (9)	23 (20)	0 (0)	12 (10)	117
Anencephaly	39 (68)	7 (12)	8 (14)	0 (0)	15 (26)	0 (0)	3 (5)	57
Cephalocele	0 (0)	1 (20)	1 (20)	0 (0)	1 (20)	0 (0)	2 (40)	5
Meningocele	2 (18)	4 (36)	4 (36)	5 (45)	1 (9)	0 (0)	2 (18)	11
Spina bifida	20 (45)	15 (34)	11 (25)	5 (11)	6 (14)	0 (0)	5 (11)	44

*General practitioner was able to record more than one diagnostic or screening test, thus the total number of responses was greater than 165. AFP = α -fetoprotein, MRI = magnetic resonance imaging.

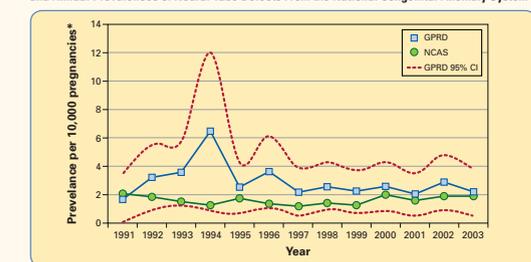
- Among returned questionnaires, 32% (n = 52), of responders used the GPRD electronic medical records (codes and free-text) as the only source to confirm the diagnosis.

Table 4. Neural Tube Defects by Linked Pregnancy Outcomes* for Validated Neural Tube Defects in the General Practice Research Database

	Pregnancy Event Type Matched To Neural Tube Defect						Total n	Percentage
	Still-birth n	Termination n	Miscarriage n	Pre/Postmort n	Live Birth/Delivery n			
Anencephaly	0	27	15	0	2	44	50.6	
Cephalocele	0	2	1	0	1	4	4.6	
Meningocele	0	1	0	0	5	6	6.9	
Spina bifida	2	9	8	1	13	33	37.9	
Total	2	39	24	1	21	87		
%	2.3	44.8	27.6	1.2	24.1			

*Linked pregnancy outcomes are those NTD cases identified from either a mother's or a child's record where the mother and baby were linked using the GPRD mother-baby link algorithm.

Figure 2. Estimated Prevalence of Neural Tube Defects in the General Practice Research Database and Annual Prevalences of Neural Tube Defects From the National Congenital Anomaly System*



*Pregnancies include live births, stillbirths, and elective terminations.

DISCUSSION

Strengths

- We identified and subsequently confirmed a large number of NTDs in the GPRD that will be useful in investigating maternal exposures and NTD outcomes.
- Our study reinforces the need for continued use of validation of diagnoses within the GPRD. The added information gathered by our questionnaire allowed us to determine information that is currently unavailable solely through the electronic data.

Limitations

- The prevalences we estimated from the GPRD and those from National Congenital Anomaly System are comparable in the later years, yet appear to differ in the early years.
- We were unable to adequately differentiate cases in which the mother had spina bifida from new cases of spina bifida in offspring.
- We found fewer prenatal diagnostic tests in mothers' records than we would have expected based upon the frequency of NTD pregnancy terminations and the established guidelines for antenatal care.

CONCLUSIONS

Our identification algorithm was useful in identifying three of the four types of NTDs studied. Additional information is necessary to accurately identify cases of spina bifida. We hope that this group of validated cases can be used to study the association of medication exposures during pregnancy and NTDs.

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