Review article/Pregledni prispevek

EUROCAT – EPIDEMIOLOGICAL SURVEILLANCE OF CONGENITAL ANOMALIES IN EUROPE

EUROCAT – EPIDEMIOLOŠKO SLEDENJE RAZVOJNIH NEPRAVILNOSTI V EVROPI

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Abstract

Background *European Surveillance of Congenital Anomalies (EUROCAT) is a network of population-based congenital anomaly registries in Europe surveying more than 1.5 million births per year, or 29% of the births in the European Union. It has been collecting, analysing, and interpreting birth defects surveillance data since 1979. EUROCAT actively monitors major birth defects among infants born to mothers residents in defined European regions. Cases are ascertained from multiple sources, coded using a British Paediatric Association one digit extension, and reviewed and classified by clinical geneticists that take part in the multidisciplinary staff of the network. Epidemiological data on 95 types of congenital anomaly reported among live births, stillbirths, and terminations of pregnancy after prenatal diagnosis are recorded. EUROCAT is monitoring trends and clusters in birth defects and serves for descriptive, risk factor, and prognostic studies of congenital anomalies, including evaluation of neural tube defects prevention strategies related to the periconceptional use of folic acid supplements, and assessment of the impact of the developments of prenatal diagnosis.*

Conclusions *Congenital anomalies continue to be an important cause of morbidity and mortality in infants and children. The studies on the epidemiological characteristics of congenital defects are limited, because they require the analysis of large populations and a well-organised diagnostic network. Introduction of registries of for the surveillance birth defects enables the assessment of the impact of primary prevention and developments in prenatal screening. The registry can serve as an early warning of teratogen exposures, and act as an information centre regarding clusters, and exposures to risk factors of concern.*

Key words *congenital abnormalities; registries; population surveillance; teratogens*

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Izvleček

Izhodišča *European Surveillance of Congenital Anomalies (EUROCAT, Epidemiološko sledenje prirojenih razvojnih nepravilnosti v Evropi) je mreža evropskih registrov prirojenih razvojnih nepravilnosti, ki nadzira več kot 1,5 milijona rojstev letno oziroma 29 % vseh rojstev v Evropski skupnosti. Podatki o prirojenih razvojnih nepravilnostih se v mreži EUROCAT zbirajo, analizirajo in interepretirajo že od leta 1979. Mreža dejavno spremlja pojavljanje večjih prirojenih razvojnih nepravilnosti pri novorojenčkih mater v izbranih določenih evropskih regijah. Primeri, ki so vključeni v mrežo, se zbirajo prek več virov. Kodirani so po pravilih enoštevilčne kode British Paediatric Association (Pediatrična Zveza Velike Britanije), nato pa jih pregledajo in analizirajo klinični genetiki iz multidisciplinarne skupine strokovnjakov mreže EUROCAT. Zbirajo se epidemiološki podatki za 95 različnih tipov prirojenih razvojnih nepravilnosti tako pri živorojenih otrocih kot tudi pri mrtvorojenih plodovih in medicinsko prekinjenih nosečnostih. Na temelju podatkov se analizirajo trendi v pojavnosti posameznih skupin prirojenih razvojnih nepravilnosti, ki služijo za opisne študije, za napovedovanje dejavnikov tveganja in za prognostične študije. Sem spadajo tudi strategije za preprečevanje nepravilnosti razvoja nevralne cevi, kot je npr. preventivno jemanje dodatkov folne kisline ob načrtovani nosečnosti in ocena vpliva napredka v prenatalni diagnostiki.*

Zaključki *Prirojene razvojne nepravilnosti so pomemben dejavnik obolevnosti in umrljivosti novorojenčkov in otrok. Epidemiološke študije so omejene z dejstvi, da je potrebno v analize vključiti veliko število primerov in da je nujna dobro organizirana diagnostična mreža. Vpeljevanje registrov za nadzor prirojenih razvojnih nepravilnosti nam omogoča oceno vpliva primarne preventive in razvoja prenatalnih presejalnih testov. Prav tako register lahko služi kot zgodnje opozorilo pri izpostavljenosti teratogenom in kot informacijski center za skupine prirojenih razvojnih nepravilnosti in izpostavljenosti konkretnim dejavnikom tveganja.*

Ključne besede *prirojene razvojne nepravilnosti; registri; populacijsko sledenje; teratogeni*

Introduction

Birth defects, including chromosomal abnormalities, single gene disorders, and isolated/multiple anomalies due to teratogen exposure or of unknown origin, are the major cause of embryonic and foetal death, infant mortality, and childhood morbidity in developed countries.[1,2] Affected individuals often suffer from serious physical, mental and social consequences of their handicap. Their condition also influences their families and the community in terms of quality of life, need for services and health care costs.

Because of the public health importance of congenital defects, there has been a growing interest in defining their causes and in developing, implementing, and evaluating prevention programmes. To promote the collection of data that can be used for monitoring of birth defects, for genetic and epidemiologic studies, and for development and evaluation of prevention programmes, networks of registries for the surveillance of birth defects have been set in different parts of the world.[3–5] In Europe, European network of population-based registries for the epidemiologic surveillance of congenital anomalies (EUROCAT) began in 1979 as a concerted action of the European Commission. It is supported by the EU-Commission Public Health Directorate Programme of Community Action on Rare Diseases and acts as WHO Collaborating Centre.

The specific objectives of EUROCAT today are essentially the same as when the programme started: to provide baseline epidemiologic information on congenital anomalies in Europe, to monitor trends in incidence and to assure the continuous evaluation of the impact of prenatal diagnosis, termination of pregnancy and programs of primary prevention. The network acts as an information system that can respond quickly to unusual patterns suggestive of adverse environmental influences including food, drugs, and infections, chemical and physical agents. The database serves as a source of cases for etiologic, clinical, or health service research. Over the years EUROCAT has also functioned as a model for congenital anomalies surveillance, operating as a catalyst for the setting up of information systems throughout Europe and ensuring that these systems would collect standardized and comparable data.[6–9]

In this paper, we present an overview of methods and accomplishments of EUROCAT project.

Definition of the Population

From the start of the programme it was recognized that congenital anomalies represent an assembly of numerous, heterogeneous, individually rare conditions, and that only collection of standardized data, covering extensive geographical areas will ensure high quality information that can be pooled together into large dataset, analysed, and compared between regions and countries. In addition, collection of data at the European level gives the opportunity to share kno-

wledge and funds, and to produce common policies regarding important public health issues concerning birth defects.[7]

The population covered by EUROCAT has grown over the past three decades and now includes 43 registries from 20 European countries and covers 1.5 million births per year, a 29% of births in Europe.

The EUROCAT registries are population-based, defined according to the residence of the mother in order to avoid biases due to hospital selection of high–risk pregnancies, specific pathology etc. Coverage of residents who deliver outside the monitored geographic region is also needed, because it influences data as well. The meaningful interpretation of data always requires complete knowledge of the local situation. For that reason detailed description of each registry is available at EUROCAT website.[10]

Case definition and ascertainment

The registries include information about livebirths, foetal deaths with gestational age ≥ 20 weeks, and terminations of pregnancies following prenatal diagnosis. The goal is to extend registration after the neonatal period to at least one year of age in order to collect valid information on the late-manifesting congenital anomalies (e.g. heart defects), but at this stage not all registries are able to perform this task.

All structural malformations, chromosomal aberrations, and genetic syndromes are included in the database. There is a list of minor anomalies that are to be excluded unless occurring in combination with other major anomalies. Minor anomalies can be of importance especially in cases of suspected dysmorphic syndromes and in relation to environmental effects, but there is as yet little standardization in their definition and reporting.

Cases are identified by treating physicians, gynaecologists, paediatricians, geneticists etc. and referred to local registries. The registries are all based on multiple sources of information and active case-finding, and include not only cases notified from clinicians at hospitals, but also birth and death certificates, cytogenetic reports, and post-mortem examinations. Use of multiple source case ascertainments ensures a more complete case recording, and more precise and accurate diagnosis.

Transmission to EUROCAT Central Registry is done once or twice per year by electronic file of individual records of all cases occurring in the population surveyed. Standard computer data entry and validation programme are available. In total 80 variables are recorded concerning socio-demographic status, mother and child, diagnosis, exposure, and family history.[11]

Coding and Classification

All participating registries use the common nomenclature and coding system of the tenth revision of the International Classification of Diseases (Q codes) with a more detailed extension of British Paediatric Association Classification of Diseases.[12, 13] The McKusick classification is used in addition for conditions with Mendelian inheritance. For each affected infant, information is collected on up to 8 major malformations, and a syndrome can be coded with specific code if available. Cases are reviewed at the EUROCAT Central Registry by clinical geneticists for accuracy and completeness. A group of experts in Coding and Classification Committee assists in the classification of multiple anomalies into specific patterns (genetic syndromes, sequences, associations, and complexes).

Quality Control

Diagnostic accuracy, comprehensiveness of notifications and the effect of confounding variables are continuously checked. To evaluate the completeness and accuracy of data collection EUROCAT is following parameters that serve as indication of completeness of case ascertainment (total congenital malformation prevalence, prevalence of NTD, prevalence of selected cardiac malformations, prevalence of selected postnatally diagnosed malformations, prevalence of nonchromosomal syndromes, and malformed foetal deaths), completeness of information, and accuracy of diagnosis (percentage of multiple malformations excluding chromosomal or syndrome cases, percentage of foetal deaths and terminations of pregnancy with post mortem examination, percentage of chromosomal cases with a karyotype, percentage of non-chromosomal/non-syndrome multiple malformation cases with known karyotype).

Confidentiality

Registry activities always raise the issue of confidentiality and protection of individual privacy. The EUROCAT Central Registry receives anonymous data with local serial number for each case for the use in communication with the local registry if additional information or further investigation is needed. In this way a direct approach to the infant or its parents is prevented. Strict safety measures are established to prevent unauthorized use of the records.

European countries adhere to the general principles recommended by the Assembly of the European Science Foundation in a 1980 statement concerning the protection of privacy. Special regulations apply also in some countries to the transmitting of computerized information across international borders. In addition, EUROCAT registries respect all local regulation regarding medical databases in each country.

Data Analysis and Dissemination

Analysis of collected cases, calculation and interpretation of prevalence rates, trends and cluster evaluation is done at central level. For computer import/export of data, statistical surveillance of trends and clusters and data validation a special computer programme is available [EDMP Program version 4.16 (01/10/2008)].[11]

Prevalence data on 95 congenital anomaly subgroups in 25 full member EUROCAT registries are presen-

ted on the EUROCAT website.[10] Data on major birth defects are analysed biannually for changes in birth defects rates. The total reported prevalence of congenital anomalies, including live births, stillbirths, and induced abortions, is increasing over time, from 17.3 (1980–1989) to 18.7 (1990–1999) and 20.3 (2000–2007) per 1000. This is mainly due to the better and timely diagnosis of internal anomalies, and better recording of terminations of pregnancies.[7]

Each year EUROCAT performs statistical monitoring for trends and clusters in time in order to detect signals of new or increasing teratogenic exposures which may require public health action. Some congenital defects show a steady increase in total prevalence over years (e.g. Down syndrome, gastroschisis, hypospadias).[14–16] Geographic variation within Europe is evident for a number of anomalies, including e.g. oral clefts, and omphalocele. Special report on statistical results, and the results of preliminary investigations of trends and clusters made by registries is also accessible at the EUROCAT website.[17]

One important use of EUROCAT data is the evaluation of the effectiveness of primary prevention**.** EUROCAT is following the progress in the development and implementation of public health policies to raise periconceptional folate status in women of reproductive age, analysing in the same time the prevalence of NTD in the registries in order to determine the extent to which these preventive measures are effective. Despite the fact that national policies of folic acid supplementation are in place in half of the EU member states, the prevalence of NTD in Europe has not declined substantially in the past decade and monitoring of future policy developments is needed .[18, 19]

The objective of EUROCAT is also to assess the impact of developments in prenatal screening and this was done continuously.[20–23] A special report on Prenatal Screening Policies in Europe available among publications on the web site describes the policies of prenatal diagnosis in EU countries.[24]

There has been a continuous increase in the proportion of congenital malformations that are diagnosed prenatally, and EUROCAT studies have shown significant regional differences in prenatal detection rates in Europe. Such variation may result from underlying policy, individual uptake influenced by cultural differences, and differences in quality of prenatal health services.[25] These trends are further followed and analysed.

Surveillance data from EUROCAT have been used to address other important public health issues, such as drug consumption, maternal diseases and occupational hazards during pregnancy. [26–28] EUROCAT data have also allowed the conduct of studies on the descriptive epidemiology of birth defects, evaluation of potential teratogenic exposures, and examination of possible etiologic factors contributing to birth defects.[29–31]

Conclusions

Congenital anomalies continue to be an important cause of morbidity and mortality in infants and children, but the available knowledge on causes, diagnosis, possibilities of prevention and treatment of many congenital defects is still inadequate. The studies on the epidemiological characteristics of congenital defects are limited, because they require the analysis of large populations and a well-organised diagnostic network. Introduction of registries for the surveillance of birth defects enables the assessment of the impact of primary prevention and developments in prenatal screening. The registry can serve as an early warning of teratogen exposures, and act as an information centre regarding clusters, and exposures to risk factors of concern.

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