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Nationwide investigation of multiple malformations

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A nationwide programme for the evaluation of 1,339 newborns with multiple malformations (about 8% of all malformed babies) notified to the Hungarian Congenital Malformation Registry in the period 1973 to 1975, was launched on January 1st, 1973. As specific syndromes and anomalads, 696 cases (51.9%) were notified. On the basis of individual malformations, 87 cases were identified from 439 patients with notified associations, and 27 multiple malformations among 172 stillborns and infant deaths were recognized from autopsy records collected from pathologists. 341 surviving infants were officially referred to 'multiple malformation centres' for special examination. 57 infants of 129 cooperating families were identified. Benefits of this programme are (i) the proportion of specific syndromes and anomalads increased by 12.8%; (ii) the rate of unspecified multiple malformations decreased by 56.6%; (iii) examination of multiple malformations may be the most sensitive means to detect teratogens; (iv) 50.5% of the expected number of chromosome abnormalities in newborns was found; (v) the nationwide material of multiple malformed babies offers a possibility to clarify gene abnormalities and new syndromes.

Prevention is obviously better than cure and this axiom justifies the effort for mass, selective and multiphasic screening programmes [7]. But even after the manifestation of a disease, the accurate aetiological diagnosis may help to prevent recurrence and this particularly true for genetic and teratogenic anomalies.

The Hungarian Congenital Malformation Registry records the occurrence of malformations diagnosed and compulsorily notified from birth to the age of 1 year [1]. The recorded point prevalences at birth of all malformed babies and total congenital malformations were 33.6—34.6 and 29.6—31.4 per 1000 total births, resp., in the period 1972—1975. According to this Registry and the separate Monitor, the newborns with multiple (three or more different) malformations (MMs) represent a special category of congenital malformations.

(1) The occurrence of MMs is low, 7.5—8.5% of all notified congenital malformations, which means a point prevalence at birth of about 2.6—2.9 per 1000 total births;

(2) The majority of MMs is severe: 45.0% died in the infant period and further 6.9% were stillborn. (The completeness of recording fatal cases was nearly 100%.) There is, of course, a positive correlation between the severity of MMs and the completeness of their notification. According to

our estimation e.g. about 75% of Down syndromes are notified [4].

(3) MMs involve an extremely high number of various entities (perhaps over 1000), therefore the recognition of specific MMs is difficult and rare.

(4) Identification of MMs by the investigation of their localized malformations and history often allows to determine the aetiology.

Expectations

In the knowledge of the features of MMs, a programme was launched for nationwide processing and special evaluation of MMs data in Hungary on January 1st, 1973. This was facilitated by the following facts.

(i) In Hungary, 99% of deliveries take place in hospitals.

(ii) All infant deaths and the majority of stillborns are necropsied.

(iii) The registry of severe and visible MMs is practically complete.

The following purposes were defined for the programme.

(a) Nearly all known environmental factors, so-called teratogens (rubella, ionizing radiation, thalidomide, etc.) affecting humans produce MMs. Thus the monitoring and special evaluation of MMs seems to be the most sensitive means to detect a 'cluster' caused by old or new teratogens as soon as possible.

(b) Numerical and gross structural abnormalities of the autosomes and XO aberrations usually cause generalized malformations. Thus the majority of all chromosome abnormalities may probably be discovered by chromomosome analysis of the infants with MMs. (In the near future chromosome screening of all newborns cannot possibly be organized in most countries.)

(c) Most gene abnormalities show characteristic syndromes. (The localized manifestation is an exception to the rule [2].) Thus, evaluation of a national material of MMs may help to gain experience in syndromology [6] and to identify the specific syndromes accessible to prevention by genetic counselling.

This paper presents the most important data of the nationwide processing and special evaluation of 1,339 newborns with MMs (anomalads [5], specific malformation syndromes, associations and unspecified MMs) born in Hungary in the period 1973—1975 and notified up to March 31st, 1976 (Table I).

Results

1) 695 anomalads and specific syndromes were notified (51.9% of the total material). They were all included in the evaluation study. (Reliability of the notified diagnosis is difficult to estimate. Chromosome analysis in a representative sample of Down syndrome consisting of 110 cases, confirmed trisomy 21 in 92 children (83.6%) [4].

2) 439 MMs were notified, mentioning the individual malformations without the name of anomalads or syndromes. An attempt has been

TABLE I

Data and procedure of multiple malformation investigation in Hungary, 1973—1975

Notifications of specified anomalads and syndromes are accepted for evaluation

Anomalad	Syndrome				Associations + random combinations	Unspecified multiple malformations	PRE-Total
92; 6.9%	603; 45.0%				439; 32.8%	205; 15.3%	1339; 100.0%
	Monogen	Chromosome	Teratogen	Specified unknown origin	An attempt has been made to identify these cases on the basis of		
	118; 8.8%	473; 35.3%	9; 0.7%	3; 0.2%			
72	13	—	—	0	← Malformation reported	Detailed necropsy record	Specific clinical and laboratory examinations
17	3	3	1	—	← answered: 112		
1	11	37	13	1	← cooperated: 129		
							POST-total
182; 14.3%	145; 11.4%	513; 40.3%	23; 1.8%	4; 0.3%	317; 24.9%	89; 7.0%	1273; 100.0%
	685; 53.8%						66 Not multiple

made to recognize them on the basis of the combination of malformations described. E.g. abdominal muscle deficiency, dilatation of ureters and bladder with or without cryptorchidism were accepted as 'abdominal muscle deficiency anomalad', or posterior cleft palate, glossoptosis and micrognathia were assessed as 'Robin anomalad'. In this way 87 cases, 6.5% of the total material, could be classified.

Evaluation of the remaining 557 infants with associations and unspecified 'multiple' malformations (mentioned as "multiple", "syndrome", "monster" etc.) was continued in two directions.

3) Stillbirths and infant deaths were evaluated through correspondence: detailed necropsy records completed by personal opinion concerning the aetiology were collected from the pathologists. 172 such cases occurred among 557. The pathologists were requested to cooperate in 141 cases and suitable information was obtained in 112 cases. (31 cases had such a detailed description in the notification card that it did not seem worth-while to request further data.) Anomalads and syndromes could be classified in 27 cases. 49 unspecific MMs were promoted to associations. The detailed description revealed that 29 cases were not MMs.

4) Infants supposed to have survived beyond the neonatal period were officially invited to one of the six so-called "multiple malformation centres" organized for this programme. Each centre is provided with paediatricians interested in syndromology, genetics and teratology, and laboratory facilities (chromosome, serological, e.g. rubella, CID, toxoplasmosis, certain biochemical and immunological examinations) in order to establish the correct diagnosis in patients from 3—5 counties. 341 infants were referred to these specialists. In 44 cases, involving 3 or more malformations such as talipes, congenital dislocation of the hip, torticollis, scoliosis and congenital inguinal hernia, this examination did not seem reasonable, therefore the parents were not requested to cooperate. In 32 cases the address was incorrect. 129 families (41.7%) out of the remaining 309 cases presented their infants. The cause of the poor cooperation may have been the serious condition of the infant, the indifference of parents, etc. 57 MMs out of 129 were identified. Chromosome analysis was particularly effective in the Budapest centre. Attempts failed to identify any of known syndromes or anomalads in 41 cases; 20 infants had no MM.

(Detailed tables of anomalads and syndromes caused by gene abnormalities and environmental factors as well as of associations classified according to cardinal malformations will be sent at request.)

Pros and cons of the Programme

The main problems are as follows.

(i) The questionable reliability of specified diagnosis in newborns with MM notified to the Registry.

(ii) The incompleteness of notification, mainly in the mild or internal MMs.

(iii) The poor cooperation of parents in special examinations.

(iv) Infants notified with 2 malformations and therefore excluded from this study may nevertheless have MM.

(v) Syndromology is still a field unsettled in many respects (e.g. the classification of MMs is an unsolved problem in general, and particularly in the ICD VIIIth and IXth revision).

The benefits were as follows.

1. The proportion of specific syndromes and anomalads has increased by 12.8% (171 cases). Specification and especially the knowledge of the aetiology may be important in view of the estimation of prognosis and recurrence risk as well as for specific treatment and prevention.

2. The reliability of the MMs registry has improved significantly: the rate of unspecified MMs decreased by 56.6%, and 66 'no MM' were excluded.

3. Detection of a cluster of specific malformation syndromes helps to reveal teratogens. E.g. an obvious correlation was found between the 1974 rubella epidemic and the increased frequency of the combination of cataract, congenital heart defect and other malformations (Fig. 1).

4. 50.5% of the expected number of chromosome abnormalities could be detected (Table II). At first sight this proportion seems to be low, but several circumstances have to be taken into consideration. Thus, only peripheral blood cultures were performed; some severely affected infants died before the examination; several infants with MM have not been recognized and/or notified; the so-called minor malformations and functional anomalies, e.g. mental subnormality, are not or cannot be registered till the age of 1 year; few infants were taken to the centres for special examination.

5. The diagnosis of structural chromosomal abnormalities and recessive syndromes led to the detection of carriers. Alone in the Budapest centre 12 balanced chromosome abnormalities were found.

6. The nation-wide processing of MMs may offer a possibility to find new syndromes, to clarify the aetiol-

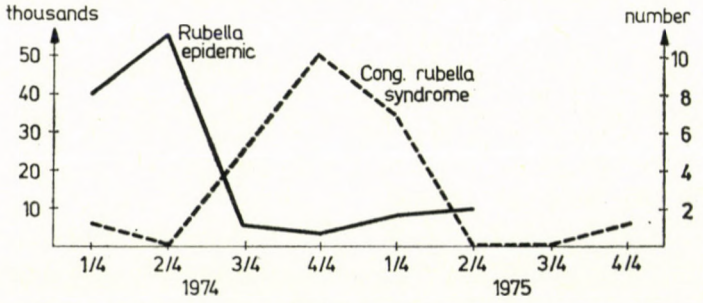

FIG. 1. Increased number of congenital rubella syndrome after rubella epidemic in Hungary 1974

TABLE II

Result of chromosome analyses*

Recognizable chromosome syndromes in infants	Occurrence among 55,679 newborns (per cent)	Expected figure (n = 540,045) No	Observed figure No	Per cent
Down	0.11	594	467**	78.6
Patau	0.005	27	11	40.7
Edwards	0.01	54	8	14.8
Deletions	0.01	54	5	9.3
Other structurals***	0.05	270	10	3.7
XO	0.003	16	12	75.0
Total	0.198	1015	513	50.5

* data of 7 well-known newborn studies in Arhus, Boston, Calgary, Edinburgh, Moscow, New Haven, Ontario-Winnipeg
** not all cases proved by chromosome analysis
*** including inversions and supernumerary markers

ogy of some others and to improve our knowledge of syndromology.

As far as we know this attempt was the first to organize a nationwide and partly follow up evaluation of MMs. (MMs were studied with a national register of malformations in Sweden [3].) A first attempt is always prone to imperfections but may allow to gain experience that makes this improved programme worth continuing and will perhaps encourage to establish similar ones.

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