MALTA CONGENITAL ANOMALIES REGISTER

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HALF YEARLY REPORT JULY - DECEMBER 1998

DOWN SYNDROME

Down syndrome or Trisomy 21 is quoted as the most frequent single cause of mental retardation. For this reason the condition is of significant social and public health importance especially today when, in society, all efforts are being made for individuals with Down syndrome to live a normal life.

GENETIC ASPECTS OF DOWN SYNDROME[1]

Down Syndrome is a chromosomal disorder whereby individuals have an extra chromosome 21 in the nuclei of their body cells. Hence the term Trisomy 21.

In about 94% of cases, Down syndrome results from non-disjunction in the first or second meiotic division occurring in one of the parents. Maternal non disjunction occurring in the first meiotic division may be the result of a prolonged period of chromosome pairing, corresponding to maternal age. Other types of non-disjunction may result from a defect in the attachment of the spindle to the chromosomes. Approximately 20% of cases occur in the paternal chromosomes. Non disjunction occurring in the second meiotic division is likely to be the same in both sexes. The maternal age effect in such cases may be attributable to a decreased sensitivity of the maternal uterus in detecting a trisomic fetus. Non disjunction in the zygote occurs in about 2.5% cases and gives rise to mosaic trisomy 21.

Data from different studies suggest that the overall risk for parents having a second child with Down syndrome is approximately 0.5% in the case of free trisomy 21. In the Maltese population this would be expected to once in about 15 years. The recurrence risk is least in the 25-35 year maternal age group and is about twice the normal age-specific risks for mothers above or below this range. Chromosome 21 translocation carriers have a theoretical recurrence risk of 33%; empirically this is reduced to 16% if the mother is the carrier and to 5% if the father is the carrier.

Several genes have now been assigned to chromosome 21 and a phenotypic map assigning the features of Down syndrome to specific regions has also been constructed. The fundamental question still remains: how does an excess of genes, with consequent over-production of certain proteins, lead to the severe developmental disturbances observed in Down syndrome? It is likely that the features of Down syndrome are the result of interaction of the various genes causing regulatory imbalance.

EPIDEMIOLOGY OF DOWN SYNDROME - MALTA 1993-1997

The Malta Congenital Anomalies Register has a computerised data base with information regarding congenital anomalies in Malta since 1993. An analysis of this data regarding Trisomy 21 was performed.

Prevalence: During 1993-1997 there were 24,495 births to Maltese residents on the Maltese Islands[2]. Of these, 41 were registered at the registry as having Trisomy 21. This gives a total prevalence rate of 16.7/10,000 total births (or 1 in 600). This compares well with the EUROCAT (European Registration of Congenital Anomalies) average rate quoted as 16.6 per 10, 000 births.

Type of birth: Of the 41 births with Down syndrome, none were stillbirths while one died before one week of age.

Genetics: Upon analysing genetic studies, it was found that only one baby had translocation trisomy while all the others had the more common free trisomy 21. None were reported as being mosaic.

Gender distribution: In this study, from a total of 41 babies with Down syndrome, 18 (44%) were males and 23 (56%) were females, giving a male:female ratio of 1:1.3. Although in this analysis there was a predominance of female births with Down syndrome, this difference was not statistically significant. In other larger studies it is actually documented that there are more male births with Down syndrome[3].

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Parental Ages: Analysis of parental age showed that the average parental age of babies with Down syndrome was significantly higher than that of all deliveries. This was true for both mothers' and fathers' ages. The average maternal age for all deliveries was 29.2 years, while that for deliveries of babies with Down syndrome was 36.2 years. Similarly, while the average paternal age for all deliveries was 31.7 years, that for fathers having babies with Down syndrome was 38.8 years.

The variation in prevalence of Down Syndrome by maternal age group is given in the table below.

Prevalence of Down syndrome in different maternal age groups - Malta 1993-1997.

Maternal age	Babies with Down synd.	Total births[2]	Prevalence / 10,000 births
<20 years	0	955	na
20-24	0	4929	na
25-29	3	8575	3.5
30-34	12	6488	18.5
35-39	17	2907	58.5
40+	9	641	140.4
TOTAL	41	24495	16.7

na - not applicable

Time of diagnosis: All 41 cases were diagnosed at or shortly after birth. Trisomy 21 can be diagnosed prenatally using maternal serum markers, chorion villous sampling and amniocentesis. Studies quote that approximately 60% of affected pregnancies may be diagnosed using a combination of maternal age and maternal serum markers as indicators[4,5]. Diagnosis may then be confirmed by amniocentesis and cytogenetic studies.

Upon analysing other EUROCAT registries' data[6], an average of 26.5% of affected pregnancies in <30 year olds were diagnosed prenatally between 1990-94, of which 74.1% were terminated after diagnosis. While 68.1% of affected pregnancies in >35 year olds were diagnosed prenatally, of which 90.9% were terminated. These rates vary between the different registries, depending on culture and availability of screening tests.

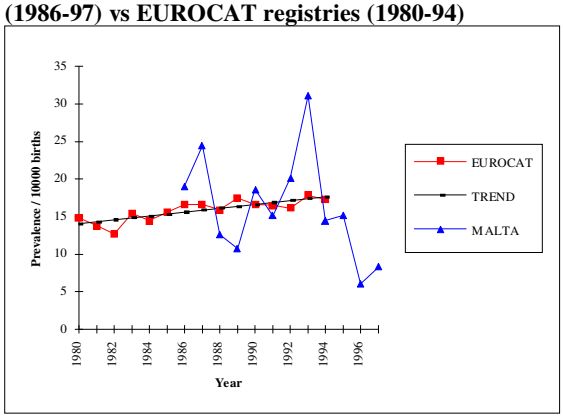
Associated anomalies: Down syndrome is frequently associated with other major defects. In this analysis, 23 (56%) of the babies had associated major anomalies. The most frequently found anomalies were congenital heart defects found in 44% of the babies. Gastrointestinal defects were found in 2 babies, one had a heart defect and renal defect, another had a diaphragmatic hernia, another a respiratory defect and another had a skin defect. These findings are similar to those of other large scale studies[7].

Trends in prevalence: The trends in prevalence of Down Syndrome in Malta over the past 10 years is shown in the figure below. No definite trend can be described, but this is not unexpected because of the small number of cases seen in Malta.

The prevalence reported in Europe using EUROCAT data however, shows a trend of increasing prevalence of the syndrome. This trend has been said to be due to increasing maternal ages at delivery. Prenatal testing can also cause an artificial increase because prenatal diagnostic methods now detect cases which formerly would have been lost by miscarriages. It has also been documented that there has been an actual increase in Down syndrome in younger mothers[8].

A study by S. Ayme in 1996, utilising EUROCAT data, states that 'the global prevalence of Trisomy 21 has increased regularly these last years as expected from the increase in mean maternal age at conception. It has doubled in the last 10 years'[8].

Trends in prevalence of Down Syndrome in Malta (1986-97) vs EUROCAT registries (1980-94)



References:

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2. Demographic Review for the Maltese Islands for the years 1993-1997. Malta: Central Office of Statistics (Annual Publications).
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4. Haddow JE. et al, Prenatal screening for Down Syndrome with maternal serum markers. NEJM, 1992; Vol. 327, 588-93.
5. Wald NJ. et al, Serum screening for Down syndrome between 8-14 weeks of pregnancy. British J. of Obs. & Gynae, 1996; Vol. 103, 407-12.
6. A EUROCAT Working Group, 15 years of Surveillance of Congenital anomalies in Europe 1980-1994, EUROCAT Report 7. Belgium, Scientific Institute of Public Health Louis Pasteur, 1997.
7. Stoll C. et al, Study of Down Syndrome in 238,942 consecutive births. Ann Genet. 1998; 41:1,44-51.
8. Ayme S., Value of Registries in Decision making in Public Health the example of Trisomy 21. Rev. Epidem Sante Publique 1996; 44 Suppl. 1, S82-9.

This report includes congenital anomalies diagnosed and confirmed in infants/fetuses born during the period July to December 1998 in Malta and Gozo and having been reported to the registry by May, 1999. All major anomalies as defined according to EUROCAT (European Registration of Congenital Anomalies) guidelines are included. Minor anomalies are reported only when they occur in combination with major anomalies.

Total number of infants/fetuses diagnosed with major congenital anomaly

Hospital		Total births*		With Congenital anomaly	
		Livebirths	Fetal Deaths	Livebirths	Fetal Deaths
St. Luke' s Hosp.	M	1038	4	39	0
	F	950	7	27	0
Gozo Gen. Hosp.	M	74	1	5	0
	F	95	2	2	0
Private Hosp.**	M	122	2	2	0
	F	120	0	0	0
Total		**2399**	**16**	**75**	**0**

*Provisional data from Maternity Information System (KGH), hospital records & National Mortality Register
** Private Hospitals include: Capua Palace Hospital, St. James' Hospital and St. Philip' s Hospital.

Distribution of infants/fetuses according to number of major anomalies

Anomalies	Number of infants/fetuses
Isolated major anomaly	44
Two or more major anomalies of same system	18
Major anomalies involving two different systems	5
Major anomalies involving three or more different systems	1
Chromosomal anomalies	5
Other congenital malformation syndromes and malformations NEC	2
Total	**75**

Distribution of infants/fetuses with major congenital anomalies according to system/s involved

ICD code	System	Number of infants/fetuses			Fetal deaths
		Total	Males	Females	
Q00-Q99 Congenital malformations, deformations and chromosomal anomalies					
Q00-Q01	Neural tube defects	0	0	0	-
Q02-Q07	Other nervous system defects	6	2	4	-
Q10-Q18	Eyes, ears, face and neck	1	1	0	-
Q20-Q28	Cardiovascular	26	11	15	-
Q30-Q34	Respiratory	1	1	0	-
Q35-Q37	Cleft palate and lip	2	1	1	-
Q38-Q45	Digestive system	1	1	0	-
Q50-Q56	Genital organs	6	6	0	-
Q60-Q64	Urinary	4	3	1	-
Q65-Q79	Musculoskeletal deformities	12	10	2	-
Q80-Q85	Skin & Integument	0	0	0	-
Q86-Q89	Other congenital malformation syndromes and malformations NEC	2	2	0	-
Q90-Q99	Chromosomal anomalies	5	4	1	-
	Two different systems	5	2	3	-
	Three or more different systems (not recognised as a syndrome or sequence)	1	1	0	-
Other Anomalies*					
D18	Haemangioma, lymphangioma any site	3	1	2	-
	Total Infants with anomalies	**75**	**45**	**29**	

* These anomalies are not tabulated in EUROCAT reports

The table overleaf gives a breakdown of all the major anomalies registered in babies born between July and December 1998. In this table:

- Hydrocephaly occurring with spina bifida is not included
- Spina bifida occulta is reported only if there are complications or when it occurs in combination with major defects
- Confirmed glandular / coronal / 1st degree hypospadias is not registered unless in combination with major defects.
- Skin tags, naevi, angiomas, hemangiomas, glomus tumors, lymphangiomas and birthmarks less than 4 cms^2 are not registered unless in combination with major defects.

Other minor anomalies as defined by EUROCAT guidelines are also not registered unless in combination with other major defects.

		Total	Male	Female
Q00-Q01	**Neural Tube defects**	**0**	**0**	**0**
Q02-Q07	**Other anomalies of nervous system**	**6**	**3**	**3**
Q03.9	Congenital hydrocephalus	3	2	1
Q04.9	Congenital malformation of brain, unspecified	1	0	1
Q05	Lumbosacral spina bifida	2	1	1
Q10-Q18	**Anomalies of the eye, ear, face and neck**	**2**	**1**	**1**
Q17.0	Accessory auricle	1	0	1
Q17.3	Other misshapen ear	1	1	0
Q20-Q28	**Anomalies of cardiovascular system**	**51**	**22**	**29**
Q20.1	Double outlet right ventricle	1	0	1
Q20.3	Transposition of great vessels	1	0	1
Q20.4	Double inlet ventricle	1	0	1
Q21.0	Ventricular septal defect	12	5	7
Q21.1	Atrial septal defect	23	9	14
Q21.3	Tetralogy of Fallot	1	1	0
Q22.1	Congenital pulmonary valve stenosis	3	1	2
Q23.0	Congenital stenosis of aortic and mitral valves	1	1	0
Q25.0	Patent ductus arteriosus	5	2	3
Q25.1	Coarctation of the aorta	1	1	0
Q25.6	Stenosis of pulmonary artery	2	2	0
Q30-Q34	**Anomalies of respiratory system**	**1**	**1**	**0**
Q31.4	Congenital laryngeal stridor	1	1	0
Q35-Q37	**Cleft lip and cleft palate**	**5**	**3**	**2**
Q35.3	Cleft soft palate	1	1	0
Q35.5	Cleft hard palate with cleft soft palate	2	1	1
Q35.7	Cleft uvula	1	1	0
Q37.8	Unspecified cleft palate with cleft lip, bilateral	1	0	1
Q38-Q45	**Anomalies of digestive system**	**1**	**1**	**0**
Q42.2	Congenital abscence/atresia/stenosis of rectum	1	1	0
Q50-Q56	**Anomalies of the genital organs system**	**10**	**10**	**0**
Q53.1	Undescended testicle (assoc. with other defects)	1	1	0
Q54.0	Glandular hypospadias (assoc. with other defects)	1	1	0
Q54.1	Hypospadias, penile	5	5	0
Q54.4	Congenital chordae	2	2	0
Q54.9	Hypospadias, unspecified	1	1	0
Q60-Q64	**Anomalies of the urinary system**	**7**	**6**	**1**
Q60.4	Renal hypoplasia, bilateral	1	1	0
Q61.0	Congenital single renal cyst	1	1	0
Q62.0	Congenital hydronephrosis	1	1	0
Q62.1	Atresia and stenosis of ureter	1	0	1
Q62.3	Other obstructive defects of renal pelvis and ureter	1	1	0
Q62.7	Congenital vesico-uretero-renal reflux	1	1	0
Q64.2	Congenital urethral valves	1	1	0
Q65-Q79	**Deformities of the musculoskeletal system**	**18**	**14**	**4**
Q65.1	Congenital dislocation of hip, bilateral	1	1	0
Q66.0	Talipes equinovarus (structural)	2	2	0
Q66.4	Talipes calcaneovalgus	1	1	0
Q67.2	Dolicocephaly	1	1	0
Q69.0	Accessory finger(s)	4	3	1
Q69.2	Accessory toes	2	1	1
Q70.3	Webbed toes	1	1	0
Q71.3	Congenital abscence of hand and fingers	2	1	1
Q72.3	Congenital abscence of foot and toes	1	0	1
Q77.4	Achondroplasia	1	1	0
Q77.8	Other osteochondroplasia	1	1	0
Q79.0	Congenital diaphragmatic hernia	1	1	0
Q80-Q85	**Congenital anomalies of the skin & integument**	**3**	**1**	**2**
Q82.5	Congenital non-neoplastic naevus (>4cm^2)	3	1	2
Q86-Q89	**Other congenital anomalies / multiple anomalies**	**2**	**2**	**0**
Q87.0	Malformation syndromes affecting facial appearance	1	1	0
Q87.8	Other specified congenital malformation syndromes	1	1	0
Q90-Q99	**Chromosomal anomalies**	**6**	**5**	**1**
Q90.0	Down syndrome/Trisomy 21, meiotic nondisjunction	5	4	1
Q95.8	Other balanced chromosomal rearrangements	1	1	0
Other major anomalies registered		**8**	**6**	**2**
D18	Haemangioma / Lymphangioma any site	3	1	2
E03.1	Congenital Hypothyroidism	1	1	0
H50.0	Convergent concomitant strabismus	1	1	0
K07.0	Micrognathism	1	1	0
K42.9	Umbilical hernia NOS (assoc. with other defects)	1	1	0
P94.2	Congenital hypotonia	1	1	0