MALTA CONGENITAL ANOMALIES REGISTER

HALF YEARLY REPORT JANUARY - JUNE 1998

FACIAL CLEFTS
GENETICS AND EPIDEMIOLOGY

Embryological outline

During the fifth week of development the face develops from three processes:

1. The frontonasal process in the midline extending from the forebrain to the stomodeum (primitive mouth). It gives rise to the midline structures of the face from forehead to lip. It also induces the development of the underlying forebrain. In its lower part it forms bilateral the nasal prominences surrounding the nasal pits, and a midline intermaxillary segment which gives rise to the philtrum of the upper lip, part of the upper jaw bearing the incisor teeth and the primary palate.
2. The maxillary process above the stomodeum
3. The mandibular processes below the stomodeum.

The embryological palate which separates the nasal cavities from the mouth consists of two parts. The primary palate, develops in week 6 and fuses with the maxillary processes; the secondary palate develops from the lateral palatine processes which grow from the maxillary processes during week 7 and fuse in the midline above the tongue by week 12.

Clefts of the primary and secondary palate, formerly called cleft lip and cleft palate respectively, result from a failure of fusion of these rudiments.

Cleft secondary palate (cleft palate) results from failure of fusion of the palatal shelves across the midline. Cleft secondary palate varies in extent and includes cleft hard palate, cleft uvula and submucous cleft palate which is not detected by simple inspection.

Cleft primary palate (lateral cleft lip) results from failure of fusion of the maxillary process with the lateral nasal fold. The cleft is situated lateral to the philtrum of the lip and runs obliquely to the nasal cavity. It is sometimes accompanied by cleft secondary palate which arises as a secondary defect. Bilateral clefts of the primary palate may also occur and are separated in the midline by the philtrum.

Epidemiology

Cleft primary palate (cleft lip) whether or not accompanied by cleft secondary palate, is etiologically distinct from cleft secondary palate alone. In EUROCAT registries over the period 1990-1994, the global prevalence rate for cleft primary palate (cleft lip) with or without cleft secondary palate was 8.9 per 10,000 births of which 4% occurred in stillbirths; the global prevalence rate of cleft secondary palate alone was 6.4 per 10,000 births of which 5% occured in stillbirths. In Malta the corresponding rates were 6.5 and 8.4 per 10,000 births respectively. During the period January 1993 to April 1998 there were 51 cases of facial clefts in Malta. They were analysed in relation to their sex distribution, and whether occurring with other anomalies or as isolated defects. The results are shown in table 1.

Table 1 - Facial clefts in Malta during the period January 1993 to April 1998.

		Cleft primary +/- secondary palate.		**Cleft secondary palate**		
		Male	Fe-male	Male	Fe-male	Indet sex
Total number	n	17	5	16	12	1
	Sex ratio	3.4 : 1		1.3 : 1		
Associated with other anomalies	n	5	3	2	5	1
	%	29%	60%	12%	42%	100%
	Sex ratio	1.7 : 1		0.3 : 1		
Isolated defects	n	12	2	14	7	-
	%	71%	40%	88%	58%	
	Sex ratio	6 : 1		2 : 1		

There is a 3:1 predominance of males over females in cleft primary +/- secondary palate and an almost equal male to female ratio in

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cleft secondary palate alone. The male predominance is even more marked for cases of isolated cleft primary +/- secondary palate where the ratio is 6:1. Associated anomalies occurred more frequently in cleft primary palate +/- secondary palate (36%) than in cleft secondary palate alone (28%) and more frequently in females than in males. For cleft primary +/- secondary palate 60% of females and 29% males had other associated anomalies; for cleft secondary palate alone 42% of females and 12% of males had other associated defects.

Genetics

The genetics of isolated cleft primary and secondary palate is complex and heterogeneous. In general it is often assumed to follow a multifactorial pattern of inheritance with variable influence of genetic and environmental factors. However, it may also follow the model of a major mutant gene whose effects may be modified by additional polygenic variation and environmental influences. For practical purposes empiric recurrence risks are used. These vary according to the number of affected sibs and affected parents as shown in the table below which is adequate for general counselling purposes. However, the risks are also affected by the severity of the cleft and the sex of the affected individual. Interestingly, although cleft primary palate (cleft lip) occurs much less frequently in girls, the recurrence risk for affected girls is greater than that for affected boys.

Table 2 - Empiric recurrence risks for cleft primary +/- secondary palate & cleft secondary palate alone occurring as isolated anomalies

		Cleft primary+/- secondary palate	Cleft secondary palate
Normal parents	+1 affected sib	4%	3.5%
	+2 affected sibs	14%	13%
1 affected parent		4%	3.5%
	+1 affected sib	12%	10%
	+2 affected sibs	25%	24%
Both parents affected		35%	25%

It should be emphasised that these recurrence risks apply only to cleft primary and secondary palate occurring as isolated defects. As noted above about 30% of clefts are associated with other congenital defects. About 200 dysmorphology and chromosome syndromes include cleft lip and / or palate as a feature in the phenotype. In such cases the recurrence risks would be those of the syndrome itself. It is therefore important to establish a precise diagnosis for the purpose of genetic counselling and to exclude the presence of associated anomalies or syndromes before falling back on the above quoted empiric risks. An important example is the association of cleft lip +/- cleft palate with pits or mucous cysts on the lower lip (Wan der Woude syndrome) which is autosomal dominant with vertical transmission from parents to offspring and 50% recurrence risks. The lower lip pits may be very inconspicuous and easily overlooked. Rarely, isolated cleft lip-palate without any apparent lip pits may be inherited as an autosomal dominant condition. This condition is also exceptional in that some affected individuals may have cleft palate only.

Median Cleft Lip

Median cleft lip results from hypoplasia of the fronto-nasal process. Median cleft lip is distinguished from bilateral cleft lip by the absence of the philtrum in the midline.

Median cleft lip, which is to be distinguished from bilateral cleft lip, is a completely different entity which, in almost all cases, is a defect of development of the fronto-nasal process as part of the holoprosencephaly sequence. The holoprosencephaly sequence includes a whole spectrum of abnormalities ranging from midline cleft lip to absence of the nose and cyclopia (fusion of the eyes due to absence of the nasal cavity separating them). These defects are often associated with severe anomalies of the brain, which are usually hypoplasia of the frontal lobes (causing trigonocephaly) and absence of the corpus callosum). This defect may be induced by teratogens and is also part of some chromosome syndromes, mostly trisomy 13 and deletion of the short arm of chromosome 18.

Cleft face

Cleft face may be considered as a more severe form of cleft lip in which the failure of fusion is more extensive and extends up to the orbit. It is very rare. When it occurs it is usually the result of a disruption e.g by amniotic bands and is invariably accompanied by other severe congenital defects.

(Submitted by Prof. A. Cuschieri - Dept. of Anatomy, University of Malta)

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This report includes congenital anomalies diagnosed and confirmed in infants/fetuses born during the period January to June 1998 in Malta and Gozo and having been reported to the registry by August 1998. 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	885	6	22	1
	F	843	1	32	0
Gozo Gen. Hosp.	M	108	0	3	0
	F	102	0	2	0
Private Hosp.**	M	142	0	2	0
	F	144	0	0	0
Total		2224	7	61	1

*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	45
Two or more major anomalies of same system	7
Major anomalies involving two systems	5
Major anomalies involving three or more systems	1
Chromosomal anomalies	4
Other congenital malformation syndromes and malformations NEC	0
Total	**62**

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		**58**	**27**	**31**	**1**
Q00-Q01	Neural tube defects	2	1	1	1
Q02-Q07	Other nervous system defects	2	1	1	-
Q10-Q18	Eyes, ears, face and neck	1	1	0	-
Q20-Q28	Cardiovascular	30	10	20	-
Q30-Q34	Respiratory	0	0	0	-
Q35-Q37	Cleft palate and lip	3	3	0	-
Q38-Q45	Digestive system	1	0	1	-
Q50-Q56	Genital organs	2	1	0	-
Q60-Q64	Urinary	2	1	1	-
Q65-Q79	Musculoskeletal deformities	6	4	2	-
Q80-Q85	Skin & Integument	0	0	0	-
Q86-Q89	Other congenital malformation syndromes and malformations NEC	0	0	0	-
Q90-Q99	Chromosomal anomalies	4	2	2	-
	Two different systems	5	2	3	-
	Three or more different systems (not recognised as a syndrome or sequence)	1	1	0	-
Other Anomalies*					
H55 - H59	Disorders of eye and adnexa	1	0	1	-
E00 - E07	Disorders of thyroid gland	1	0	1	-
P37	Cong. infections and parasitic diseases	1	0	1	-
	Total Infants with anomalies	**62**	**28**	**34**	**1**

* These anomalies are not tabulated in EUROCAT reports

Anomalies registered for infants born from January -June '98 (as reported by August '98)

		Total	Male	Female
Q00-Q99 Congenital malformations, deformations & chromosomal abnormalities		**80**	**37**	**43**
Q00-Q01	**Neural Tube defects**	**3**	**1**	**2**
Q00.0	Anencephaly	3	1	2
Q02-Q07	**Other anomalies of nervous system**	**3**	**1**	**2**
Q03.9	Congenital hydrocephalus	2	1	1
Q05.7	Lumbosacral spina bifida, unspecified	1	0	1
Q10-Q18	**Anomalies of the eye, ear, face and neck**	**2**	**2**	**0**
Q13.3	Congenital corneal opacity	1	1	0
Q17.4	Misplaced / low set ears	1	1	0
Q20-Q28	**Anomalies of cardiovascular system**	**45**	**16**	**29**
Q20.3	Transposition of great vessels	2	1	1
Q21.0	Ventricular septal defect	13	4	9
Q21.1	Atrial septal defect	19	7	12
Q21.3	Tetralogy of Fallot	1	1	0
Q22.1	Congenital pulmonary valve stenosis	4	1	3
Q22.4	Congenital tricuspid stenosis	1	0	1
Q22.5	Ebstein' s anomaly	1	0	1
Q25.0	Patent ductus arteriosus	2	0	2
Q25.1	Coarctation of the aorta	1	1	0
Q25.6	Stenosis of pulmonary artery	1	1	0
Q30-Q34	**Anomalies of respiratory system**	**0**	**0**	**0**
Q35-Q37	**Cleft lip and cleft palate**	**3**	**3**	**0**
Q35.5	Cleft hard palate with cleft soft palate	1	1	0
Q36.0	Cleft lip, bilateral	1	1	0
Q37.1	Cleft hard palate with cleft lip	1	1	0
Q38-Q45	**Anomalies of digestive system**	**1**	**0**	**1**
Q39.2	Tracheo-oesophageal fistula	1	0	1
Q50-Q56	**Anomalies of the genital organs system**	**2**	**2**	**0**
Q54.4	Congenital chordae	1	1	0
Q54.9	Hypospadias, unspecified	1	1	0
Q60-Q64	**Anomalies of the urinary system**	**3**	**2**	**1**
Q61.4	Renal dysplasia	1	0	1
Q62.0	Congenital hydronephrosis	1	1	0
Q64.6	Congenital diverticulum of bladder	1	1	0
Q65-Q79	**Deformities of the musculoskeletal system**	**14**	**8**	**6**
Q65.1	Congenital dislocation of hip, bilateral	1	1	0
Q66.0	Talipes equinovarus (structural)	1	0	1
Q68.1	Congenital deformity of hand	1	1	0
Q68.8	Other specified cong. Musculoskeletal deformities	1	1	0
Q69.0	Accessory finger(s)	2	1	1
Q70.0	Fused fingers	1	0	1
Q70.3	Webbed toes	3	1	2
Q70.4	Polysyndactyly	1	1	0
Q76.4	Other cong. Malformations of the spine	1	1	0
Q79.0	Congenital diaphragmatic hernia	1	1	0
Q79.2	Exomphalos / Omphalocele	1	0	1
Q80-Q85	**Congenital anomalies of the skin & integument**	**1**	**1**	**0**
Q82.5	Congenital non-neoplastic naevus	1	1	0
Q86-Q89	**Other congenital anomalies / multiple anomalies**	**0**	**0**	**0**
Q90-Q99	**Chromosomal anomalies**	**4**	**2**	**2**
Q90.0	Down syndrome/Trisomy 21, meiotic nondisjunction	2	0	2
Q90.9	Down syndrome/Trisomy 21, NOS	1	1	0
Q91.3	Edward syndrome/Trisomy 18, unspecified	1	1	0
Other anomalies reported		**3**	**0**	**3**
H55	Congenital Nystagmus	1	0	1
E03.1	Congenital Hypothyroidism	1	0	1
P37.1	Congenital Hydrocephalus due to toxoplasmosis	1	0	1

NB: 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.