CENTRAL NERVOUS SYSTEM ALFORMATIONS DETECTED IN PALESTINIAN NEWBORNS

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CNS MALFORMATIONS

The incidence of major CNS malformations detected in the neonatal period was calculated on the last consecutive 33969 hospital deliveries.
All cases of >500 gms and or >22 weeks gestational age were included. The incidence of all CNS malformation was 9.27 per 1000 births and the incidence of NTD was 5.18/1000 births. Different aspects of these results and their limitations are discussed.

Anencephaly was defined as congenital malformation characterized by total or partial absence of the cranial vault, the covering skin and the brain.

Spina bifida was defined as a herniation or exposure of the spinal cord and/or meninges through an incompletely closed spine.

Encephalocele was defined as a protrusion through a cranial defect and such a protrusion may be only a cerebrospinal fluid filled meningeal sac or may contain neural tissue.

Meckel-Grubber syndrome was considered as the association of occipital meningocele, polycystic kidneys and polydactyly inherited as autosomal recessive character.

Hydrocephaly is a heterogeneous entity. In this study we considered the diagnosis when the head circumference was enlarged with the presence of ventricular dilatation or with abnormally enlarged ventricles even if the head circumference was not enlarged yet.

If no other intracranial malformation like **Dandy Walker or absent corpus callosum** or other extra CNS malformation was found the hydrocephalus was classified as **isolated**.

Cases of hydrocephaly associated with NTD were not considered under hydrocephaly.

Colpocephaly was considered when the volume of the frontal horns was nearly normal and there was major dilatation of the occipital horns without absence or evident hypoplasia of corpus callosum and in the absence of NTD or Arnold-Chiari malformation.

Hydranencephaly is a condition of uncertain origin characterized by an intact skull and absence of cerebral hemisphere.

Holoprosencephaly is a malformation in which the prosencephalon has failed to undergo segmentation and cleavage into paired symmetric cerebral hemispheres.

Microcephaly was considered in this series when the head circumference was at least 3 standard deviations below the mean for gestational age. Only evident and confirmed cases of **craniostenosis** were included in this series. Sirenomelia cases were only included as caudal regression in this series.

Dermal sinuses were not considered as major CNS malformations in this study.

In addition we did not include other malformations like Klippel-Feil and arthrogryposis among CNS malformations, the later is a quiet common malformation among this population.

Malformations associating CNS anomalies with chromosomal aberration were considered with chromosomal aberrations.

DIAGNOSIS

Diagnosis of cases was based on the following:

1- Antenatal clinical and ultrasonic findings (on admission for delivery or during regular antenatal care).

2- Clinical examination at birth, during the first week of life till discharge from the neonatal unit (in some cases up to eight weeks).

3- Postnatal brain ultrasound examinations, brain axial computerized tomography and plain roentgenograms.

4- The family authorized autopsy in few cases.

5- In cases of hydrocephaly and microcephaly mother and baby serum were tested for evidence of toxoplasmosis and cytomegalovirus.

6- Metabolic workup and chromosomal studies were done upon clinical indications.

RESULTS

The general characteristics of the studied series were given in precedent chapters.

I- The Importance of CNS Malformations among Stillbirths and Neonatal Deaths

Among the 730 stillborns, 156 (21 %) had a severe congenital anomaly which could explain their death. One hundred four out of the 156 malformed stillborns had a major CNS anomaly (67% of the total malformed stillborn).

Eight hundred twenty eight newborns died during the first 28 days of life, 306 (37%) of these deaths were due to severe malformations and 151 (18.24% of neonatal deaths) were due to major CNS anomalies.

Table I

	N	MNB	CNS M	% CNS/TM	% CNS-M/T
TB	33969	812	309	38	0.91
SB	730	156	104	67	14
LB	33269	656	205	31	0.62
ND	828	306	151	49	18.24
PND	1558	462	255	55	16.7

The total number of perinatal deaths in this series (>22 weeks gestational age or >500 gms) was 1558 (4.57 %), among the 462 total number of malformed ones (29.6% of perinatal deaths) 255 were associated with major CNS anomalies (16.7 % of perinatal deaths).

II- CNS malformations

A- General overview of CNS anomalies

During the period of the study 812 (23/1000) products of delivery with major malformations in all systems were registered.

These malformations represent 38% of all malformations (major and minor) registered in the same period. Among the major malformations 309 cases were severe malformations of the CNS diagnosed antenatally or in the first week of life.

General distribution of CNS anomalies is shown in table II.

The total incidence was 9.1 per 1000 births for all CNS malformations considered in the study.

Table II
GENERAL DISTRIBUTION OF CNS ANOMALIES

MALFORMATION	M	F	TX	SB	ND	M /1000 D	M /N DEL
NTD	77	99	176	62	100	5.18	193
Hydrocephaly	64	48	112	42	44	3.297	303
Craniostenosis	3	4	7	0	0	0.206	4853
Microcephaly	4	6	10	0	3	0.294	3397
Hydranencephaly	1	1	2	0	2	0.058	16985
Caudal Regression	0	2	2	0	2	0.058	16985
T CNS	149	160	309	104	151	9.096	110
T Malformed newborns	449	363	812	156	306	23.90	41.8
% of CNS/all malformed NB			**38.05**	**66.66**	**49.34**		

B- Neural tube defects (NTD)

Neural tube defects represented the major part, (57%) of CNS malformations. Male to female ratio was 1:1.3 in this group.

Hydrocephaly was associated with myelomeningocele and encephalocele in 65% of cases. Few newborns with myelomeningocele and encephalocele have also other major malformations (Table III). Results demonstrated that a newborn with NTD was encountered every 193 deliveries with equal figures for anencephaly and myelomeningocele.
Cases of spina bifida occulta were not included in this study as major malformation. Meckel-Gruber syndrome although a form of encephalocele was put in a distinct group.

Table III
DISTRIBUTION AND INCIDENCE OF NTD

MALFORMATION	M	F	TX	SB	ND	M/1000 D	M/N DEL
Anencephaly	**31**	**39**	**70**	**37**	**33**	**2.060**	**485**
Myelomeningocele	**30**	**40**	**70**	**14**	**42**	**2.060**	**485**
Omphalocele	0	1	1	1	0		
Imperforated anus	1	0	1	0	1		
Cloacal exstrophy	1	0	1	0	1		
Meckel-Gruber S	**8**	**10**	**18**	**6**	**12**	**0.529**	**1887**
Encephalocele	**7**	**9**	**16**	**5**	**11**	**0.471**	**2123**
Absent nose	1	0	1	0	1		
Cleft palate	0	1	1	0	1		
Warburg	1	0	1	0	1		
Iniencephaly	**1**	**1**	**2**	**0**	**2**	**0.058**	**16985**
Total NTD	**77**	**99**	**176**	**62**	**100**	**5.18**	**193**
T CNS	**149**	**160**	**309**	**104**	**151**	**9.096**	**110**

Mother's age of stillborn and newborns with and without NTD were compared (Table IV), and a clear increase of the incidence of NTD with the mother age was noted (chi square for linear trend $p<0.0001$). No such trend was noted with other CNS malformations.

Age at delivery was in about 60% under 25 years, only 1% of mothers have age of more than 40 years in this series. This young mother age is to be considered in the interpretation of results. All

parents of Meckel-Gruber syndrome cases were consanguineous and half of the cases were in fact recurrences. The rate of consanguinity among parents of other NTD cases was comparable to the rate of consanguinity in the whole group (57% of first and second-degree cousins).
No significant seasonal variation in the incidence of NTD or other CNS malformations was found when the date of conception of malformed and non-malformed babies.

Table IV
AGE OF MOTHER WITH AND WITHOUT NTD

AGE	WITHOUT NTD	WITH NTD	%NTD	TB	%TB
<20	9800	33	18.75	9833	28.94
20<25	10814	47	26.704	10861	31.97
25<30	7435	42	23.863	7477	22.01
30<40	5374	48	27.272	5422	15.96
>40	370	6	3.4090	376	1.106
T	**33793**	**176**	**100**	**33969**	**100**

Chi square for linear trend 26.4, p=<0.0001

<u>C- Hydrocephaly</u>

Hydrocephaly is the major single malformation. One newborn with hydrocephaly was encountered in every 300 deliveries without considering cases associated with neural tube defects.

Male to female ratio was 1.3:1 in the whole group and 1.1:1 in the isolated hydrocephaly group.

Hydrocephaly was considered isolated when no other significant malformation or other significant structural brain anomaly was noticed except ventricular dilatation. One case of hydrocephaly due to congenital toxoplasmosis was diagnosed during the period of the study.

Cases of hydrocephaly associated with other significant malformation or having a particular brain structural anomaly were considered in a distinct subgroup.

Extended families of isolated cases of hydrocephaly are still under investigation for the presence of recurrence, NTD, and other malformations.

Two of the cases of colpocephaly were brother and sister, who had been followed for 6 and 8 years; they had moderate speech delay. Corpus callosum was present but reported as thin in these cases.

Table V
HYDROCEPHALY CASES GROUP

MALFORMATION	M	F	TX	SB	ND	M/1000D	M/N DEL
Hydrocephaly-Isolated	**44**	**39**	**83**	**36**	**36**	**2.443**	**409**
Hydrocephaly +	**20**	**9**	**29**	**6**	**8**	**0.854**	**1171**
Colpocephaly	2	2	4	0	0	0.117	8492
Dandy Walker	5	1	6	1	3	0.176	5662
Absent C. callosum	2	1	3	0	0	0.088	11323
Klipple-Trenaunay	1	0	1	0	0		
Cleft lip palate	1	0	1	0	1		
Cleft lip	1	2	3	2	0		
Cardiac	2	0	2	0	0		
Warburg	0	1	1	0	1		
TEF+ ambiguous Genitalia	1	0	1	1	0		
TEF+ imperforate anus	1	0	1	0	1		
Others	4	2	6	2	2		
Hydrocephaly-total	**64**	**48**	**112**	**42**	**44**	**3.297**	**303**
T CNS	**149**	**160**	**309**	**104**	**151**	**9.096**	**110**

D- Other CNS anomalies

Three of the severe cases of microcephaly reported were associated with esophageal atresia. Parents were first degree cousins in 2 cases. One of the cases was operated at birth and survived for six months without increasing her head circumference. Brain CT showed small lateral ventricles and smooth cortex with atrophic frontal lobes. Autopsy was refused. Up to our knowledge this association of microcephaly and esophageal atresia was not reported as an autosomal recessive entity.

Table VI

MALFORMATION	M	F	TX	SB	ND	M/1000 DEL	M/N DEL
Craniostenosis	**3**	**4**	**7**	**0**	**0**	**0.206**	**4853**
-Isolated	3	3	6	0	0		
-TEF+Crouzon	0	1	1	0	0		
Microcephaly	**4**	**6**	**10**	**0**	**3**	**0.294**	**3397**
-Isolated	1	5	6	0	0	0.176	5662
-Cleft palate	1	0	1	0	1		
-TEF	1	2	3	0	2		
Hydranencephaly	**1**	**1**	**2**	**0**	**2**	**0.058**	**16985**
Caudal Regression	**0**	**2**	**2**	**0**	**2**	**0.058**	**16985**
Total	**8**	**13**	**21**	**0**	**7**		
T CNS	**149**	**160**	**309**	**104**	**151**	**9.096**	**110**

DISCUSSION

The relatively high number of deliveries registered in Makassed Hospital (15-20 % of deliveries in the studied area), the non-existence of a general policy to refer suspected cases of CNS malformations to this hospital could make the sample to a certain extent representative of the prevailing situation of CNS malformations in spite of the limitations inherent to hospital based studies.

It is worthy to mention that there is no formal law or established social practice for termination of malformed fetuses and medical practice in this field is still without consensus in the community. In addition the practice of autopsy needs family consent, the number of authorization is still very limited. The main hospital stay of mothers delivering "normal" babies is 36 hours; this short stay might have resulted in under detection of certain malformations.

CNS major malformations represented 38% of the total major malformations detected in the neonatal period. This high figure might reflects an increase in the incidence but the fact that major CNS malformations can be diagnosed more easily than cardiac or other malformations, in the condition of the study, is to be taken into consideration.

Among the NTD the incidence of encephalocele is quiet high in this series. Encephalocele and encephalocele associated with Meckel-

Gruber syndrome occurred as 1/1000 deliveries which is 5 times of that reported in the literature as nearly stable incidence (1). We have no explanation for these results. We deliberately decided to compare our results with older series published in the medical literature in order to have significant comparisons as the antenatal diagnosis and abortion have certainly made comparisons more difficult with modern series from developed countries.

The incidence of hydrocephaly in this study, although not including cases associated with NTD, is one of the highest reported in the word literature (2, 3, 4).

Ethnic variations of CNS malformations were widely reported, but it is still difficult, at times, to separate ethnic and geographic variations from that due to differences in reporting systems (1).

The decrease of NTD incidence is largely documented in USA and European countries. (5, 6). The reasons for this phenomenon are beyond the scope of this discussion.

The different methodology of calculation of rates between different studies, inclusion of still births, ascertainment of cases, and the laps of time between them must be taken into consideration when comparing results. In USA study of (7) Myraiantopolos & Shung, which included stillbirths, the reported incidence of major CNS malformations were 83.2/10000, which represented only 10% of all major malformations. The incidence of CNS malformations in this series is approximately the same incidence of CNS malformation (93.3/10000) reported from Edinburgh (8).

COMPARISON WITH REGIONAL FIGURES

Most of data reported from our region (Arab world and Israel) were focused on the incidence of NTD.
Stevenson et al in 1966 reported through a study organized by the WHO in 16 countries CNS and NTD malformations recorded at birth (2). Data from Alexandria (Egypt) was the only one which concerned a neighboring Arab population to be reported, the rate of major CNS malformations was 78.23/10000 and that of NTD was 56.4 per 10000.
A hospital study including live and stillbirths in Saudi Arabia reported an NTD incidence of 1.6/1000 birth (9). In an earlier study the rate of spina bifida was 1.1/1000 births in the northern part (Tabuk) and 0.4

in a southern city (Khamis), the climatic difference between the two areas was suggested as a factor for this variation (10). In Kuwait the incidence of anencephaly declined from 3.2/1000 in 1968 to 1.33/1000 in 1983 (11). In Lebanon (Beirut) the incidence of anencephaly was 2/1000 (12). Damyanov and Dutz (1971) reported the incidence of anencephaly as 1.6/1000 births in Shiraz -Iran (13). Some of the Israeli studies included limited numbers of Palestinians (non-Jews). Halevi (14) reported the results of a pilot study on reported cases of all congenital malformations diagnosed at birth over 2 years (1959-1960). Spina bifida and meningocele rate was 0.74/1000 births and anencephaly rate was 0.61/1000 births. Congenital hydrocephalus 0.59/1000. No specific significant data is reported about "non Jews".

Using death registration and hospital records, L Naggan in 1971 studied reported cases of NTD between 1958-1968 including still borns among Jewish population (infants born to Jewish mothers) (15). The prevalence of anencephaly was 0.86/1000 and 0.6/1000 for spina bifida.

Results from Jerusalem perinatal (16) study pointed out a difference in the rate of NTD between Palestinians (Arabs) and Jews. The overall rate of major malformations was 37.5/1000. It was 36.7 for Jews and 66.7 for Palestinians. NTD was 1/1000 among Jews and 2.6/1000 among Palestinians, the authors noted that the number of Arabs included in the study was small but other unpublished data confirm the higher incidence of NTD among Palestinians. Other CNS malformations considered together were 1.5/1000.

More recently, Merlob et al reported their results from the 4 Israeli hospitals affiliated with the International clearing house for Birth Defect Monitoring System (17). These results indicated that the prevalence of spina bifida has increased from 0.11/1000 births in 1978 to 0.74/1000 in 1986. Anencephaly rate increased from 0.27/1000 in 1978 to 0.66/1000 in 1981 then started to decrease again down to 0.28 in 1986. The authors think that these results, taking into consideration the perinatal screening and elective abortions may indicate a real increase in the prevalence of NTD in the central part of Israel. Only one percent of this studied group was "non Jewish".

The population studied in our series lives nearly in the same area, but no such a trend could be described by lack of sufficient data.

SEX RATIO

The predominance of females has been reported in most of the studies on NTD, mainly among anencephalic cases (18, 19, 20). Sex ratio (% of males/total) was 0.44 for anencephaly in this series; it was reported as 0.23 in Belfast, (21), 0.40 in France (20), 0.38 in Saudi Arabia (9) and 0.44 in Israel (15). Naggan suggested a higher percentage of males among population with lower risk of NTD; this finding has been confirmed by Frecker and Fraser (22) who reported in Newfoundland a tendency for the proportion of females among anencephalic births to increase with increasing frequency of anencephaly.

For spina bifida and encephalocele, sex ratio was 0.43 in our series compared with 0.38 in Belfast (21); it was 0.44 in Saudi Arabia (9) and 0.42 in Israel (15).
For hydrocephaly the situation is different concerning sex predominance. Males represented 56% of all cases of hydrocephaly and 55% of the defined isolated group in our study. Other types than X-linked hydrocephaly has been reported among Arab and Palestinian populations (23, 24). Our impression that hydrocephaly of autosomal recessive pattern of inheritance is common in Palestinian population and this hypothesis is still under investigation in our group.

AGE, PARITY SEASONAL VARIATIONS AND NTD

An increase in the incidence of NTD according to the mothers' age was clearly demonstrated in the studied series. A birth order effect was noted in other studies (25, 26) and Naggan 1971(15) concluded that, on the whole, a higher NTD risk was probably associated with an increased mother age. Few studies had found some seasonal variations in the incidence of NTD. A higher incidence was reported by Stoll et al 1988 when conception occurred during April, October, November and December (27). Such variations were not noticed in this series.

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