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ARTICLE

Epidemiology of Holoprosencephaly: Prevalence and Risk Factors

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The wide variation in cerebral and facial phenotypes and the recognized etiologic heterogeneity of holoprosencephaly (HPE) contribute to the observed inter-study heterogeneity. High lethality during the early stages of embryonic and fetal development makes HPE detection age dependent. By reviewing 21 HPE epidemiologic articles, the observed prevalence rate differences can be largely explained by the pregnancy outcome status of the studied cohort: livebirth, stillbirth, and terminations of pregnancy (TOPs): lower than 1 per 10,000 when live and still births were included, higher when TOPs were included, and between 40 and 50 per 10,000 in two classical Japanese studies on aborted embryos. The increasing secular trend observed in some studies probably resulted from an increasing use of prenatal sonography. Ethnic variations in birth prevalence rates (BPRs) could occur in HPE, but the available data are not very convincing. Higher BPRs were generally observed in the less favored minorities (Blacks, Hispanics, Pakistanis), suggesting a bias caused by a lower prenatal detection rate of HPE, and consequently less TOPs. Severe ear defects, as well as microstomia, were part of the spectrum of HPE. Non-craniofacial anomalies, more frequently associated with HPE than expected, were genital anomalies (24%), postaxial polydactyly (8%), vertebral defects (5%), limb reduction defects (4%), and transposition of great arteries (4%). The variable female predominance, found in different HPE studies, could also depend on the proportion of early conceptions in each study sample, as males are more likely to be lost through spontaneous abortions.

KEY WORDS: holoprosencephaly; prevalence; time variation; geographical variation; gender; ethnicity; associated malformations

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INTRODUCTION

The ultimate aim of epidemiologic studies of any congenital anomaly is to identify risk factors capable of guiding public health strategies for prevention. With a maximum observed prevalence rate of 1:250 conceptions [Matsunaga and Shiota, 1977], holoprosencephaly (HPE) is considered as the most frequent central nervous system defect in humans. However, relatively few epidemiological studies have been performed on HPE at older gestational ages, and so far no definitive risk factor has been clearly proved to be associated with HPE.

The main challenge in summarizing published epidemiologic studies on HPE derives from applying varying definitions. The anatomical brain defect named HPE has a precise definition: it occurs when the prosencephalon fails to cleave sagittally into cerebral hemispheres, transversely into telencephalon and diencephalon, and/or horizontally into olfactory and optic bulbs [DeMyer and Zeman, 1963; Cohen, 1989a]. Nevertheless, substantial variations of the cerebral defect, as well as of the accompanying facial anomalies, exist, generating differences in the ascertainment of HPE cases. Etiologic heterogeneity also contributes to the marked differences among studies. Environmental, genetic, multifactorial, and unknown causes seem to be involved in the genesis of this condition. Several studies have excluded, or analyzed separately, the HPE cases with chromosome abnormalities, and/or with recognized monogenic syndromes. The chromosome status of a HPE patient is not easy to determine, due to their high perinatal mortality rate, and at least 10% of those with normal karyotypes have microdeletions/duplications and remain undetected by usual karyotyping. Finally, different strategies in case selection can introduce different biases in the ascertainment of cases.

Our aim was to present some common epidemiologic clues of HPE, taking into account the recognized heterogeneity among the different published case series.

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SYSTEMATIC LITERATURE REVIEW

Twenty-one articles on the epidemiology of HPE were selected for this review (Table I). Only two of them were based on examination of embryos, and one referred only to cyclopia, the most severe form of HPE. For the others, the selected populations were live and/or still births, and terminations of pregnancy (TOPs). We did not consider studies of HPE series without denominators of births or conceptions, such as those of Moog et al. [2001] and Stashinko et al. [2004]. HPE series ascertained from ultrasonographically detected congenital anomalies, such as that of Blaas et al. [2002] were also excluded. In Table I, updated from Leoncini et al. [2008], 24 HPE series from the 21 articles are shown. Three of them presented two separate HPE series: Saunders et al. [1984] and Orioli and Castilla [2007], showing different prevalences in time; and Ong et al. [2007], showing prevalence differences by race/ethnicity.

TABLE I. Twenty-Four Selected Series From a Systematic Literature Review on the Prevalence of Holoprosencephaly

Refs.	Period of study	Country	Total cases	Prevalence (×10,000 births)	Total births	CI 95%	% of TOPs
Mitani and Kitamura [1968]	ng	Japan, hospital based	ng	0.97	ng	ng	ng
Myrianthopoulos and Chung [1974]	ng	US, hospital based	ng	0.19	ng	ng	ng
Roach et al. [1975]	1970	Indiana, US	32	0.63	ng	ng	ng
Matsunaga and Shiota [1977]	1962–1974	Japan[b]	150	41.23	36,380	34.90–48.38	100.0
Saunders et al. [1984]	1976–1978	Bristol, Weston HD, UK	ng	0.69	ng	ng	ng
Saunders et al. [1984]	1979–1982	Bristol, Weston HD, UK	6	1.92	31,225	0.70–4.18	ng
Urioste et al. [1988]	1976–1986	Spain, hospital based	ng	0.56	ng	ng	ng
Mastroiacovo et al. [1992]	1978–1989	Italy, hospital based	106	0.77	1,377,793	0.63–0.93	ng
Källén et al. [1992]	Different periods	Australia, Denmark, France, Italy, Mexico, South America, Spain, Sweden	103	0.10	10,097,383	0.08–0.12	ng
Croen et al. [1996]	1983–1988	California, US	121	1.17	1,035,386	0.97–1.40	17.4
Rasmussen et al. [1996]	1982–1986	Atlanta, US	63	0.86	734,272	0.66–1.10	4.8
Whiteford and Tolmie [1996]	1975–1994	Scotland, UK	50	0.72	694,950	0.53–0.95	24.2
Olsen et al. [1997]	1984–1989	New York, US	82	0.51	1,614,166	0.40–0.63	ng
Croen et al. [2000]	1993–1996	California, US	58	0.59	986,197	0.45–0.76	17.2
Forrester and Merz [2000]	1986–1997	Hawaii, US	25	1.09	ng	ng	24.0
Bullen et al. [2001]	1985–1998	Northern Region, UK	64	1.20	531,686	0.93–1.54	59.4
Yamada et al. [2004]	1962–2001	Japan[b]	221	50.23	44,000	43.82–57.30	100.0
Chen et al. [2005]	1987–2003	Taipei, Taiwan, hospital based[c]	59	6.06	97,306	4.62–7.82	22.0[e]
Ong et al. [2007]	1995–2004	West Midlands, UK—White	78	1.48	526,056	1.17–1.85	73.9[f]
Ong et al. [2007]	1995–2004	West Midlands, UK—non-White	33	2.62	125,818	1.81–3.68	
Orioli and Castilla [2007]	1967–2000	South America, hospital based[d]	342	0.82	4,157,224	0.74–0.91	[d]
Orioli and Castilla [2007]	2000–2003	South America, hospital based[d]	179	2.16	827,968	1.86–2.50	[d]
Leoncini et al. [2008]	2000–2004	ICHBDSR	963	1.31	7,350,000	1.23–1.40	ng
Eurocat [2009] [a]	2000–2004	Europe	731	1.34	5,449,232	1.25–1.44	75.3

TOPs, terminations of pregnancy; ng, not given.

[a]EUROCAT data published in the website, only full members.

[b]Embryos.

[c]HPE with cytogenetic results.

[d]No variation among 11 South American Countries. TOPs not permitted.

[e]Prenatal diagnosis before 20 weeks of gestation.

[f]Proportion given for all ethnic groups. Two spontaneous abortions not included.

BIRTH PREVALENCE RATES (BPRs)

Not all 21 studies shown in Table I had independent data. For example, the South American data partially overlapped the studies of Källén et al. [1992], Orioli and Castilla [2007], and Leoncini et al. [2008]. Leoncini et al. [2008] referred to HPE prevalence rates among 24 surveillance systems, members of the ICBDSR, from countries of North and South America, Europe, and Australia, and the European data overlapped with those of EUROCAT, published in the website [Eurocat, 2009].

Although all 21 studies used appropriate denominators for prevalence calculations, the actual data were not always provided for the 24 HPE series (Table I). In Figure 1, we omitted six series for which the 95% confidence intervals could not be calculated [Mitani and Kitamura, 1968; Myrianthopoulos and Chung, 1974; Roach et al., 1975; Saunders et al., 1984, earlier series; Urioste et al., 1988; Forrester and Merz, 2000]; one further study, dealing only with cyclopia [Källén et al., 1992], two only with aborted fetuses [Matsunaga and Shiota, 1977; Yamada et al., 2004], and Croen et al. [2000] were omitted as well.

BIRTH PREVALENCE VARIATION IN TIME AND SPACE

The prevalence rate differences observed in Figure 1 can be largely explained by the pregnancy outcome status of the studied cohorts: livebirths, stillbirths, or TOP. The first five studies, with a birth prevalence rate (BPR) lower than 1 per 10,000, included live and still births, except for the Olsen et al. [1997] series from New York State, which included only livebirths. Studies with a HPE BPR above 1 per 10,000 included varying proportions of TOPs, except for the South American study [Orioli and Castilla, 2007]. Leoncini et al. [2008] suggested that variations in the TOP frequency among the 24 multicountry registries were important factors explaining the observed heterogeneity of HPE BPR.

The prevalence rate differences observed in Figure 1 can be largely explained by the pregnancy outcome status of the studied cohorts: livebirths, stillbirths, or TOP.

Another possible source of BPR variations was the study period. Orioli and Castilla [2007] analyzed South American data of an 19-year-period (1982–2000) and showed that the BPR doubled after 1996. Rasmussen et al. [1996] in Atlanta, and Bullen et al. [2001] in the North of England also described an increasing secular trend which probably resulted from a more extensive use of constantly improving prenatal ultrasound examinations, with better equipment, training of ultrasonographers, and accumulated experience. Furthermore, chronologic differences in these changes among countries could contribute to the observed variations in the prevalence rates of HPE across countries, as well as across socio-economic strata and other subpopulation categories.

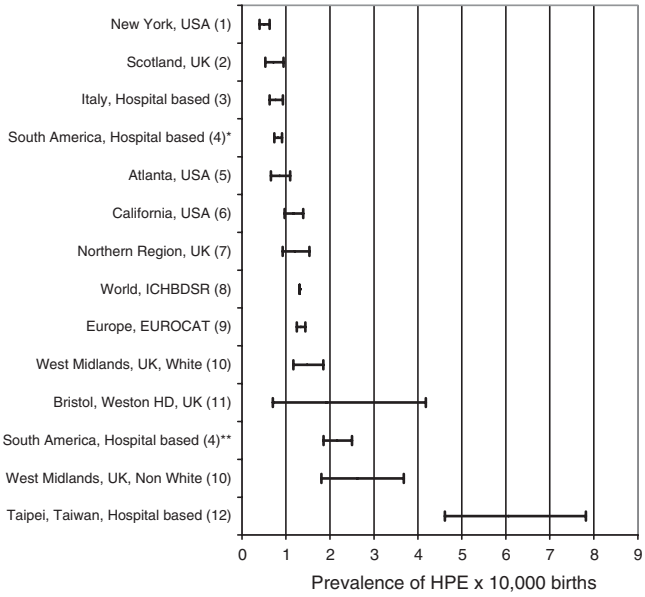

Figure 1. Frequency of holoprosencephaly in different geographical regions. (1) Olsen et al. [1997], (2) Whiteford and Tolmie [1996], (3) Mastroiacovo et al. [1992], (4) Series A* and B** in Orioli and Castilla [2007], (5) Rasmussen et al. [1996], (6) Croen et al. [1996], (7) Bullen et al. [2001], (8) Leoncini et al. [2008], (9) Eurocat [2009], (10) Ong et al. [2007], and (11) Saunders et al. [1984].

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Several multicenter studies did not find substantial BPR variations among different populations [Källén et al., 1992; Orioli and Castilla, 2007; Leoncini et al., 2008]. Nevertheless, real differences, not owing to methodological factors, can exist, as suggested by the high BPR of 6.06 per 10,000, found by Chen et al. [2005], in Taipei, Taiwan.

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Since their study only considered HPE cases with cytogenetic data, we can assume that the actual BPR was even higher than reported.

BIRTH PREVALENCE VARIATION BY ETHNICITY

Some ethnicity-related differences in HPE BPR have been described in the literature. Croen et al. [1996] described a higher risk for HPE, without chromosome anomalies, in children of White Hispanic compared to White non-Hispanic mothers in California. Since HPE cases were ascertained only among livebirths and late fetal deaths, the authors suggested that population differences in the availability of prenatal screening and subsequent TOP could partly explain the observed differences in HPE BPR. Rasmussen et al. [1996] described higher rates in non-White than in White infants in Atlanta (Georgia), but since this study did not include TOPs, the same abovementioned bias could exist.

Olsen et al. [1997] did not observe BPR differences among Whites, Hispanics, and blacks in the State of New York but they also found that Blacks were less likely to have chromosome studies done. Forrester and Merz [2000] described higher HPE BPR in infants of Far-East Asian (Chinese, Japanese, and Korean), and Filipino mothers than in those of Pacific Islanders or Whites, but the samples were small (20 cases). With data from the West Midlands Congenital Anomaly Register (WMCAR) in the UK, Ong et al. [2007] described, albeit with small numbers, a higher risk in infants of black African ($n = 3$) than non-black African ($n = 110$) mothers; they also observed a higher risk in Pakistani ($n = 19$) than in non-Pakistani ($n = 94$) mothers.

Although ethnicity-related variations in HPE BPR could exist, the actual data are not convincing. Higher rates were generally observed among less favored minorities (blacks, Hispanics, Pakistanis), suggesting a bias due to lower prenatal detection rates of HPE, and consequently less elective terminations.

TIME VARIATION

Matsunaga and Shiota [1977] suggested that more HPE cases were conceived in winter than in summer months, although the difference was not significant and could not be confirmed by others [Mastroiacovo et al., 1992]. An increasing secular trend was suggested by Saunders et al. [1984], by Rasmussen et al. [1996], and by Orioli and Castilla [2007], while Mastroiacovo et al. [1992] and Ong et al. [2007] did not find a significant secular trend. However, the first three studies partly covered an earlier period, when less prenatal information about the brain was available, and this could explain the increasing secular trends. The variations among countries would depend on the stage of technological development.

Cohen [1989a] reviewed some reported and unexplained HPE clusters. More recently, an impressive cluster of HPE and sirenomelia, with no identified cause, was described in the city of Cali, Colombia [Saldarriaga et al., 2007; Castilla et al., 2008]. While the sirenomelia cluster was statistically proven, for the concurrent cluster of HPE a random variation in the occurrence of a very rare event could not be excluded. The rarer congenital defects when analyzed in a fixed period of time present a Poisson distribution, and the apparent cluster in time can represent a common occurrence in the distribution of rare events.

PHENOTYPIC DEFINITION AND VARIATIONS

Cerebral and Facial Defects

The working definitions of HPE, incorporating inclusion and exclusion criteria, used in 18 studies are summarized in Table II. In most epidemiologic studies, the case selection was based on characteristic HPE craniofacial features and a not well-defined proportion of brain scans or autopsies. The main exclusion criterion was the absence of HPE by autopsy or radiologic imaging. We did not find any work indicating the rate of cases with a characteristic HPE face but without evidence of a holoprosencephalic brain. In consequence, none of the classic facial types of HPE, that is, cyclopia, ethmocephaly, cebocephaly, and premaxillary agenesis, used for the case selection, could be independently computed for the reviewed articles.

Table III shows the rate differences of facial and brain types among different studies. The most frequent facial types were premaxillary agenesis in some studies, and the "no facial cleft" category in others, while cyclopia and cebocephaly were third. All studies agreed on ethmocephaly as the rarest form. For the brain types, the studies showed greater similarities, with alobar HPE as the most frequent type, ranging between 40% and 75%. Semilobar was more frequent than

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lobar HPE. That all 59 HPE cases in the Chen et al. [2005] series were of the alobar type is an unusual finding. However, since they excluded cases without cytogenetic results, some selection bias could have been introduced.

The face–brain correlation principle of DeMyer et al. [1964], stating that "The face predicts the brain," weakened, as more HPE cases were described [Cohen, 1989b] and in 10–39% of the cases (Table II), there was no such clear correlation between face and brain anomaly sub-types.

ASSOCIATED UNRELATED DEFECTS

Several studies reported the frequency of associated external anomalies in

TABLE II. Material and Criteria for Holoprosencephaly (HPE) Case Ascertainment, and Reported Sex Ratios (M/F) for Holoprosencephaly (HPE) Cases

Refs.	Material	Inclusion criteria	Exclusion criteria	Sex ratio (M/F) Total HPE	Chromosomal HPE	Non-chromosomal HPE
Roach et al. [1975]	Liverborn	ng	Chromosomal anomalies	0.30	—	—
Matsunaga and Shiota [1977]	Embryos from induced abortions	Cyclopia, ethmocephaly, cebocephaly, orbital hypotelorism with a flat nose	Non-HPE after histological examination in doubtful cases	0.50	—	—
Saunders et al. [1984]	Live and still births	Minimal diagnostic criteria: orbital hypotelorism with variable features of incomplete midline development	Known chromosome trisomies	—	—	—
Urioste et al. [1988]	Liveborn	ng	ng	—	—	—
Mastroiacovo et al. [1992]	Live and still births	Diagnostic facies or a CT scan or post-mortem examination showing one of the three types of brain defect	Isolated arhinencephaly or agenesis of corpus callosum, and premaxillary agenesis without photographs or direct examination	0.77	—	—
Källén et al. [1992]	Live and still births	Cyclopia with one orbit in the middle of face and with one or two eyes	Known chromosome anomalies	0.61	—	—
Croen et al. [1996]	Live, still births, and TOP	Diagnosis of HPE, possible HPE, arhinencephaly, proboscis or single nostril, cyclopia, aprosencephaly, or holotelencephaly	Isolated partial or complete absence of corpus callosum, median cleft lip, short prolabium, arhinencephaly, hydrocephalus, encephalocele, amniotic band disruption, porencephaly, schizencephaly	0.70	0.47	0.89
Rasmussen et al. [1996]	Live, stillbirths, TOP, and infants in the 1st year of life	Severe facial defects including cyclopia, cebocephaly, ethmocephaly, proboscis, and single nostril	Brain pathologic examination or radiologic imaging demonstration of no HPE	0.73	—	—
Whiteford and Tolmie [1996]	Live, still births, TOP, and children from genetic, pathology, and pediatric neurology departments databases	HPE/arhinencephaly on CT scan or at necropsy or both	Patients with chromosomal abnormalities exclude from further analysis	—	—	0.78
Olsen et al. [1997]	Liverborn	Isolated HPE, syndromal HPE, non-syndromal HPE with multiple defects	Agenesis of corpus callosum, arhinencephaly, hydrocephalus, porencephaly, schizencephaly, and hydranencephaly not associated with HPE	0.66	0.66	0.65

(*Continued*)

TABLE II. (*Continued*)

Refs.	Material	Inclusion criteria	Exclusion criteria	Sex ratio (M/F)		
				Total HPE	Chromosomal HPE	Non-chromosomal HPE
Croen et al. [2000]	Live, still, and TOP	Diagnosis of HPE, possible HPE, arhinencephaly, proboscis or single nostril, cyclopia, aprosencephaly, or holotelencephaly	Amniotic band disruption, porencephaly, schizencephaly, and cases with a citogenetically confirmed chromosomal anomaly	0.6	—	—
Forrester and Merz [2000]	Live, still, and TOP	Confirmed diagnosis of HPE	Brain pathologic examination or radiologic imaging demonstration of no HPE	0.6	—	—
Bullen et al. [2001]	Live, still, and TOP	HPE on autopsy report, definitive prenatal or postnatal radiologic report, or a clinical geneticist's diagnosis (in conjunction with compatible reported forebrain abnormality on prenatal or postnatal scan)	Isolated arhinencephaly or agenesis of corpus callosum	0.94	—	—
Yamada et al. [2004]	Embryos from induced abortions	Characteristic cranio-facial features as closely apposed or fused eyes, proboscis, and abnormally narrow head	Same as Matsunaga and Shiota [1977]	—	—	—
Chen et al. [2005]	Live, still, and TOPs	HPE verified by perinatal ultrasound and pathology	Cases without cytogenetic results	—	0.39	1
Ong et al. [2007]	Live, still, TOP, and late fetal losses	Diagnosis of HPE confirmed clinically, radiologically or at postmortem	Isolated arhinencephaly and agenesis of corpus callosum	—	—	—
Orioli and Castilla [2007]	Live and stillbirths	Characteristic HPE cranio-facial features and/or radiologically or postmortem confirmation of HPE brain anomaly	Brain pathologic examination or radiologic imaging demonstration of no HPE	0.76	0.63	0.78
Leoncini et al. [2008]	Live + still ± TOPs	Live and stillbirths and TOPs (some countries), with diagnosis of HPE confirmed by clinical examination, autopsy, ultrasound, and/or MRI	Brain pathologic examination or radiologic imaging demonstration of no HPE	—	—	—

Ng, not given.

TABLE III. Percentage of Cerebral and Facial Defect Types in 11 Published Case Series of Holoprosencephaly

Defect	Roach et al. [1975]	Mastroiacovo et al. [1992]	Croen et al. [1996]	Whiteford and Tolmie [1996]	Olsen et al. [1997]	Croen et al. [2000]	Bullen et al. [2001]	Yamada et al. [2004]	Chen et al. [2005]	Orioli and Castilla [2007]	Ong et al. [2007]
Cerebral											
Alobar	78	62	62	64	66	40	75	100	100	40	56
Semilobar	0	26	26	33	22	33	20	0	0	43	32
Lobar	22		12	3	12	14	5	0	0	17	12
Total	100	100	100	100	100	100	100	100	100	100	100
(Total number)	(32)	(43)	(91)	(33)	(67)	(58)	(60)	(11)	(56)	(83)	(66)
Facial											
Cyclopia	0	18	13	15	15	10	—	45	29	10	—
Ethmocephaly	0	3	1	3	—	2	—	9	0	5	—
Cebocephaly	6	15	18	9	—	31	—	18	27	11	—
Premaxillary agenesis	56	43	30	24	21	10	—	27	44	25	—
No facial cleft	19	13	22	33	10	33	—	0	0	39	—
Other	19	7	15	15	—	14	—	0	0	10	—
Total	100	100	100	100	46	100	—	100	100	100	—
(Total number)	(32)	(106)	(71)	(33)	(82)	(58)	—	(11)	(59)	(174)	—

HPE cases, without discriminating between craniofacial and non-craniofacial defects. Matsunaga and Shiota [1977] found other unrelated external congenital anomalies in 46% of HPE cases. However, they included cleft lip (6.2%) and branchial arch anomalies (8.8%) which were considered by other authors as part of the spectrum of HPE defects [Mastroiacovo et al., 1992; Orioli and Castilla, 2007]. Further associated defects, reported by Matsunaga and Shiota [1977], were polydactyly (16.8%), CNS unrelated defects (14.2%), and limb anomalies (5.3%). Källén et al. [1992] found unrelated associated anomalies in 49% of infants with cyclopia; postaxial polydactyly occurred in 14.6% of the cases, and their maternal age above 35 years was more frequent than in infants with cyclopia without polydactyly. Like Matsunaga and Shiota [1977], Källén et al. [1992] considered this association as indirect evidence of undetected trisomy 13 cases.

Mastroiacovo et al. [1992] analyzed 31 HPE cases, with at least one unrelated anomaly. They described a significant association only with severe ear defects, while the observed proportions for polydactyly (12.9%) and limb reduction defects (9.7%) did not differ from random expectations. Rasmussen et al. [1996] found a 55% of non-syndromic HPE cases (n = 22) with at least one unrelated major congenital anomaly. In 64%, a concomitant skeletal or limb anomaly was observed, 50% had cardiac defects, 45% anomalies of the genital or reproductive system, 32% anomalies of gastrointestinal tract, 27% anomalies of the renal and urinary tract, and 41% polydactyly. Unlike Mastroiacovo et al. [1992], Rasmussen et al. [1996] did not test the statistical significance of these proportions.

Whiteford and Tolmie [1996] found 36% of HPE cases without chromosome anomalies had associated anomalies. Olsen et al. [1997] found a 51% of non-syndromic HPE with multiple congenital defects. Bullen et al. [2001] observed non-facial congenital anomalies in 70% of 33 euploid HPE cases; most of them were skeletal anomalies (60.6%). Chen et al. [2005]

found major structural anomalies, other than craniofacial defects, in 16% of HPE cases with normal karyotypes (n = 25): diaphragmatic hernia, omphalocele, sirenomelia with lumbar spina bifida, and hydrops fetalis, with 4% of each. Ong et al. [2007] described limb/skeletal defects in 28% of HPE cases; cardiovascular and urogenital anomalies occurred in 21% and 22%, respectively, but 85% of their HPE cases were not isolated.

Orioli and Castilla [2007] determined whether craniofacial and non-craniofacial defects in HPE cases were in excess when compared to the expected numbers. They confirmed the observation of Mastroiacovo et al. [1992] that among craniofacial defects, severe ear anomalies with atresia of the auditory canal, as well as microstomia, were part of the spectrum of HPE. Of the non-craniofacial defects, 24% of the HPE cases had genital anomalies, 8% postaxial polydactyly, 5% vertebral defects, 4% limb reduction defects, and 4% had transposition of great arteries; all these defects were significantly associated with HPE, while no significant association was found between HPE and anencephaly, spina bifida, or encephalocele. The significant association between HPE and the five groups of non-craniofacial defects was also observed by the other abovementioned studies [Matsunaga and Shiota, 1977; Källén et al., 1992; Rasmussen et al., 1996; Ong et al., 2007], although not all of the associations mentioned in those studies could be confirmed by Orioli and Castilla [2007].

Significant associations between HPE and other defects could suggest unrecognized syndromes among the HPE multiply malformed infants. Associated defects were described even in euploid HPE cases, which could mean that some syndromic HPEs without chromosome anomalies, or with cryptic anomalies [Bendavid et al., 2006a,b], are frequent enough to rise the rates of these defects among HPE cases. See Kauvar et al. [2010], Keaton et al. [2010], and Raam et al. [2010] for reviews of HPE associated with agnathia, ectrodactyly, and craniosynostosis, respectively.

Gender

Table II shows the published sex ratios of HPE cases according to the pregnancy outcome status and to the selection criteria. In South American countries, HPE was more common among females in the three categories used in the article: isolated, associated, and chromosomal [Orioli and Castilla, 2007]. However, only in the total group of 337 cases did the sex ratio differ significantly from the expected value. The numbers of isolated (182), associated (99), and chromosomal cases (56) were large enough to suggest that in that study, as well as in those of Mastroiacovo et al. [1992], and of Rasmussen et al. [1996] females were less predominant than in other studies. Other series [Roach et al., 1975; Källén et al., 1992; Croen et al., 1996, 2000; Forrester and Merz, 2000; Chen et al., 2005] showed a stronger female predominance. Some authors observed a female excess only in cytogenetically abnormal HPE cases, while in euploid cases the sex ratio was less deviated [Croen et al., 1996; Chen et al., 2005; Orioli and Castilla, 2007]. Olsen et al. [1997] found a low sex ratio in both chromosomally normal and abnormal HPE cases. Rasmussen et al. [1996] suggested as a possible explanation for the female predominance that males are more likely to be lost through spontaneous abortion. This idea was founded on studies of HPE in embryos [Matsunaga and Shiota, 1977], who showed a much higher rate of HPE than in newborns, and also on studies of fetuses with HPE, where an equal sex ratio or even a male excess could be observed [Blaas et al., 2002]. The different proportions of embryos, fetuses, stillborns, liveborns, and older infants in the study populations could explain the observed differences among studies.

In South American countries, HPE was more common among females in the three categories used in the article: isolated, associated, and chromosomal.

ASSOCIATED VARIABLES (RISK FACTORS)

Epidemiologic variables or risk factors associated with HPE are specifically discussed in other articles of this special issue [Miller et al., 2010; Johnson and Rasmussen, 2010]; therefore, only a brief comment will be made here. In the first epidemiological analysis with a representative number of cases, Matsunaga and Shiota [1977] concluded that the only positive clue to the etiology of HPE was the higher rate of previous miscarriages among mothers of HPE cases. This association could not be confirmed by Croen et al. [2000], nor by Orioli and Castilla [2007]. Instead, the latter authors showed that intrauterine growth restriction, primigravidity, and non-cephalic presentation occurred more often in HPE cases than in matched controls.

Several risk factors mentioned in the literature were in fact part of the HPE phenotypic description, such as low birth weight, prematurity, twinning, non-cephalic presentation, gestational bleeding, perinatal mortality, and associated birth defects. The lack of consensus about their association with HPE probably results from the varying proportions of etiologically different HPEs in each study population. Furthermore, some variables, not directly related with the phenotype, such as previous miscarriages, maternal drug consumption, maternal age, gender, race/ethnicity, and heritability, would probably also depend on the proportions of each etiologic HPE type, mainly that of cases with chromosome anomalies. Even the variation of the HPE BPR by ethnicity is influenced by the access of racial minorities to the health programs, and then to the possibility of TOP. Since it is not a easy task to collect all information about TOPs in the countries where they are permitted, racial/ethnic differences in HPE prevalences could occur.

CONCLUSIONS

When dealing with a congenital defect, characterized by phenotypic as well as causal heterogeneity, definitive conclusions based on different studies cannot be easily drawn.

Etiologically, HPE may be due to obvious chromosome and cryptic chromosome abnormalities, monogenic or oligogenic syndromes, as well as environmental factors, and differences in epidemiologic results basically reflect different proportions of each cause.

By refining the HPE causal definition we can expect more epidemiological clues and perhaps the inclusion of multifactorial mechanisms as an important cause of HPE.

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