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Gender Affects Clinical Suspicion of Down Syndrome

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1. Introduction

It is known that the Down syndrome phenotype can result from a triplication of a small portion of chromosome 21. In the majority of cases diagnosed as Down syndrome (90%), free trisomy for chromosome 21 is found; in some 6% of the cases translocations are observed, and about 3% are mosaics with normal cell line; other aberrations involving chromosome 21 are rare and found in less than 1% [Mikkelsen, 1988]. In a huge literature on the epidemiology of Down syndrome, there are two features undoubtedly established, a strong association of free trisomy 21 frequency with advanced maternal age, and male prevalence among patients with Down syndrome due to regular trisomy 21.

Generally, the clinical diagnosis is straightforward and well-known to all medical workers [Mikkelsen, 1988]. However, misdiagnosis (false positive diagnosis) of Down syndrome was reported in numerous publications [Ahmed et al., 2005; Baccichetti et al., 1990; Ballesta et al., 1977; Engel et al., 1970; Fried et al., 1980; Hamerton et al., 1965; Melve et al., 2008; Szollar et al., 1983], being particularly high in neonates [Devlin & Morrison, 2004; Hindley & Medakkar, 2002]. Factors which alter suspicion of trisomy 21 are known to be early delivery and prematurity [Mikkelsen, 1988].

Previous studies reported a significant female prevalence among Down syndrome patients with clinical diagnosis only which suggested that gender also may alter a suspicion of Down syndrome in infants [Kovaleva et al., 1999; Kovaleva, 2002]. Therefore, the main objectives of this study were to evaluate a rate of false positive diagnosis of Down syndrome in a large well-defined geographically population and to determine male-to-female ratio (sex ratio, SR) among patients with false-positive diagnosis.

2. Materials and methods

St. Petersburg is a large city with a population of about 5 million, and an average of 50 000 births a year. Almost all births take place in a hospital. There is one major clinical genetic unit in the city which provides the service to the target population, the St. Petersburg Centre for Medical Genetics. The overwhelming majority of live born babies suspected to have genetic disease have been examined by clinical geneticists from the Centre within the first several days after birth and prior to discharge from a hospital. Medical personnel at children hospitals and special institutions for handicapped children may also call for a clinical

geneticist for suspected genetic condition. It is mandated that few cases born in private hospitals and tested cytogenetically elsewhere, must be reported to the Centre. Older patients or their parents can arrange an appointment to the Centre themselves after being referred to by medical specialists. Only certified clinical geneticists at St. Petersburg Centre for Medical Genetics can request karyotyping to confirm or refute a suspected chromosomal abnormality.

In St. Petersburg, due to global social transition, the birth rate fell dramatically from about 73 thousand in 1987 to 29 thousand in 1999 which caused a decline in the number of live born patients with Down syndrome over time. Since 2000, the birth rate begun to increase steadily, reaching more than 50 thousand in 2009. However, at the same time, since 2000, the impact of prenatal diagnosis on the prevalence of Down syndrome prevalence has been expanding rapidly, affecting the number of live born babies with Down syndrome.

The completeness of cytogenetic confirmation of trisomy 21 varied significantly, increasing from 21% in 1970 to almost 100% currently. Therefore, for the sake of sufficient sample size, the author has chosen for the analysis the period of 1986-2009, when data completeness had begun improving from 82% in 1986 to about 100% in 1999 and upward.

All cases of Down syndrome delivered during the period January 1, 1986 to December 31, 2009 were abstracted from a population-based registry, the St. Petersburg Down Syndrome Register, founded and run by the author. The Register has been collecting data on all Down syndrome patients residing in St. Petersburg, whether diagnosed antenatally or live born since 1970. The method for data collection has been described elsewhere [Kovaleva et al., 2001].

Data on patients suspected to have Down syndrome but with a normal karyotype were retrieved from logbooks of the cytogenetic laboratory at the St. Petersburg Centre for Medical Genetics and from logbooks of the cytogenetic laboratory at the Leningrad Oblast Children Hospital which provides service to the regions surrounding St. Petersburg. The degree of certainty of the Down syndrome diagnosis was determined by presence of question mark(s) in the records of indication for karyotyping in the logbooks. When the diagnosis at clinical examination seemed obvious, the question mark was absent. In doubtful cases, sometimes up to three question marks presented in the record. In some cases, suspected mosaicism was an indication. The data obtained were analyzed using standard statistics including binomial test and Chi-square test with Yates correction.

3. Results

Over a period of twenty-four years (from 1.01.1986 to 31.12.2009), 1257 children had been referred to cytogenetic investigation for either confirmation or exclusion of trisomy 21. The Down syndrome diagnosis was confirmed in 1129 (89.8%) of them and 120 (9.5%) children had a normal karyotype. The remaining eight children with another chromosomal abnormality were excluded from the analysis (Table 1). 1119 cases of trisomy 21 were diagnosed in the St. Petersburg Centre for Medical Genetics and ten cases were diagnosed elsewhere. The sex ratio among children with confirmed DS diagnosis was skewed, with a surplus of males (612 males/517 females, SR=1.18). In contrast, among children with a normal karyotype, there was a strong female prevalence (25 males/95 females, SR=0.26), the difference is highly significant, $p \ll 0.0001$.

Neonates constituted 94% of patients with confirmed Down syndrome while a proportion of neonates among those with false positive diagnosis was appreciably smaller (65%).

Therefore a proportion of false positive cases among neonates was 6.8% compared to 35% in patients aged one month and older (Table 1). The annual rate of false positives among neonates varied from 0% in 1990, 1995, and in 2000 to 21% in 2008 (Figure 1). There was an apparent trend with an increase in false positives in relation to a reduction in the number of cases tested. This variation did not depend on the clinical experience of the referring doctors. For example, 8 of 9 false positive cases in 2008 were referred to cytogenetic testing by clinical geneticists whose experience had exceeded 15 years, and the remaining one case was suspected to have Down syndrome by a clinical geneticist with 7 years of experience.

Age of patients	True Down syndrome (trisomy 21)	False positive diagnosis		Total
		Normal karyotype	Other chromosomal abnormality	
Neonates	1063	77	6 ^a	1146
Patients under 1 yo	59	20	2 ^b	81
Patients aged 1 yo and older	7	23		30
Total	1129	120	8	1257

^a 46,XY,18p-; 46,XX,t(11;22); 46,X,t(X;16)(p11;q13); 46,XX,r(18); 46,XX, r(18); 47,XXX

^b 46,XY,add(10)(q26); 46,XX,inv(22)(p13;q12)

Table 1. Proportion of false positive diagnosis according to the patients' age at cytogenetic examination

Among false positive neonates, there was a very strong female prevalence, with 11 males/66 females, SR=0.17. Notable female predominance was also found in both patients aged under 1 year old (7 males/13 females, SR=0.54) and in older patients (7 males/16 females, SR=0.44).

Further analysis was performed regardless of the date and place of birth of the patients. Overall, a normal karyotype was diagnosed in 103 neonates (17 males/86 females, SR = 0.20, different from population value of 1.06, $p < 0.0001$), in 68 children of the age group up to 1 year old (24M/44 females, SR = 0.55, $p = 0.0052$), and in 64 children aged 1 year and older (29M/35 females, SR = 0.83, $p > 0.05$).

Data on the level of certainty in false positives cases is presented in Table 2. The diagnosis at clinical examination seemed obvious in 22% of neonates and in only 6% of children 1 year and older. In two cases, since features of Down syndrome were obvious, chromosome testing was requested twice. The proportion of suggested mosaicism was increased with the patients' age, from 3% in neonates to about 10% in the oldest group of patients. Request for excluding Down syndrome was noted in two cases only. Unquestionable Down syndrome diagnosis was stated in 20% and mosaicism was suspected in about 9% of males, while in females these figures were 14% and 4% correspondingly (Table 3).

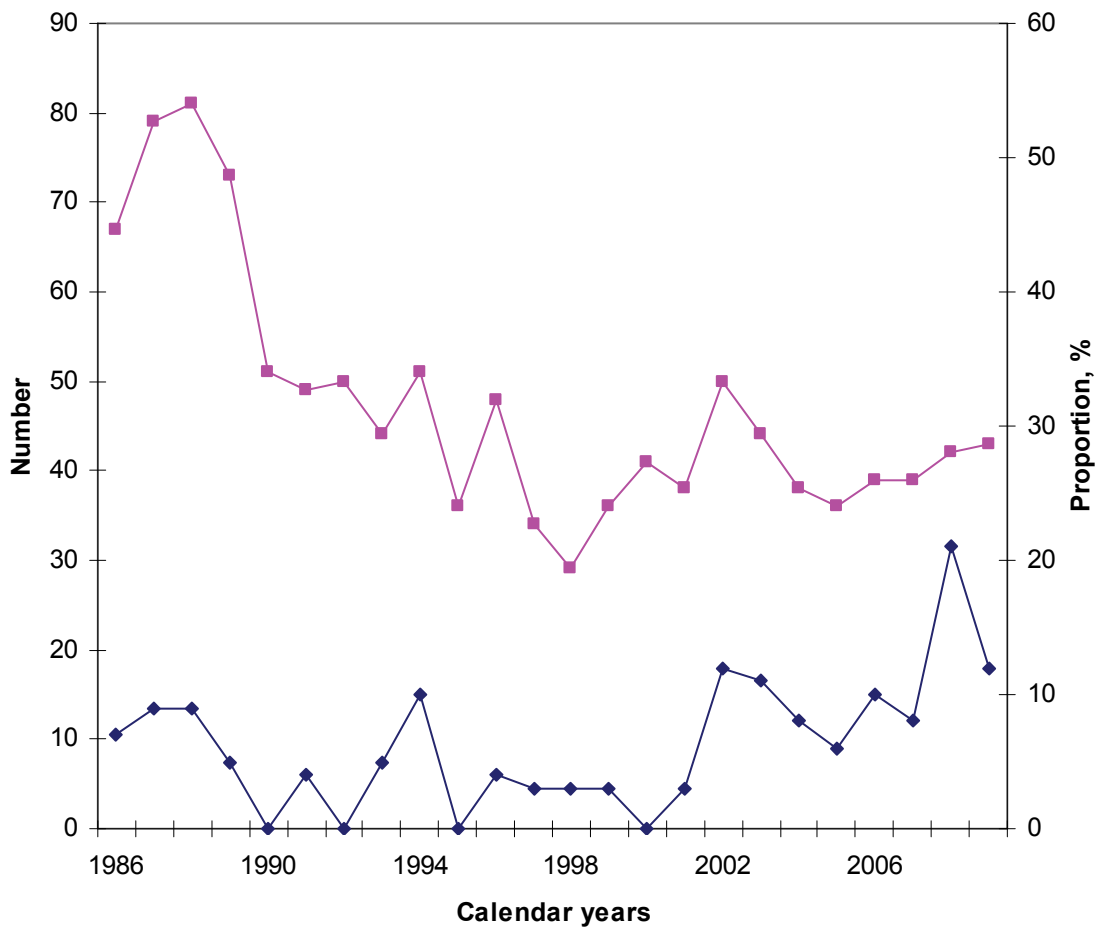


Fig. 1. Total number of cytogenetically tested cases (red line) and proportion of cases with false positive diagnosis (blue line).

Expression of certainty	Patients with false positive diagnosis of Down syndrome			
	Neonates	Under 1 yo	1 yo and older	Total
Down syndrome	22 (22%)	11 (16%)	4 (6%)	37
Mosaicism?	3 (3%)	3 (4.5%)	6 (9.5%)	12
Down syndrome?	60 (58%)	51 (75%)	53 (83%)	164
Down syndrome??	14 (14%)	2 (3%)	1 (1.5%)	17
Down syndrome???	2 (2%)	1 (1.5%)		3
Request for excluding Down syndrome	2 (2%)			2
Total	103	68	64	235

Table 2. Degree of certainty in requesting for cytogenetic testing according to the age of the patients

Expression of certainty	Patients with false positive diagnosis of Down syndrome		
	Males	Females	Total
Down syndrome	14 (20%)	23 (14%)	37
Mosaicism?	6 (8.5%)	6 (4%)	12
Down syndrome?	47 (67%)	117 (71%)	164
Down syndrome??	2 (3%)	15 (4%)	17
Down syndrome???	1 (1.5%)	2 (1%)	3
Request for excluding Down syndrome	0	2 (1%)	2
Total	70	165	235

Table 3. Degree of certainty in requesting for cytogenetic testing according to the gender of patients with false positive diagnosis

Data on distribution of both true Down syndrome patients and false positives by maternal age is presented in Table 4. The analysis of maternal age distribution in false positive patients was complicated since maternal ages were available in only a small proportion of the sample. There is some increase (13%) in the proportion of mothers aged 35 years old and older compared to general population (6% to 9%), due to a higher proportion (23.5%) of mothers of advantaged ages in the group of patients 1 year old and older. The overall figure of 13% in false positives is significantly lower compared to about 33% in true Down syndrome ($p = 0.0003$).

Maternal age	Down syndrome	Patients with false positive diagnosis of Down syndrome			
		Neonates	Under 1 yo	1 yo and older	Total
< 20	87	6	3	1	10
20-24	378	6	7	5	18
25-29	367	15	3	5	23
30-34	324	10	4	2	16
35-39	352	2	2	3	7
40+	213	1	1	1	3
Total	1721	40	20	17	77

Table 4. Maternal ages in Down syndrome and in false positive diagnosis, 1970-2009

4. Discussion

4.1 Proportion of false positive cases

Over the study period, 1129 postnatal cases of Down syndrome were identified. Regular trisomy 21 was observed in 90.9%, translocation trisomy in 5.4%, and mosaicism in 3.7% of the cases. These figures are in accordance with previous data worldwide. One hundred-twenty cases, referred for cytogenetic examination for suspicion of Down syndrome, displayed a normal karyotype, while eight children were diagnosed with another chromosome abnormality. Therefore, the proportion of misdiagnosed cases was 10.2% (128/1129). Analysis of the literature (Table 5) showed these data to be in agreement with majority of previous studies. Data from Spain [Ballesta et al., 1997] is of particular interest regarding the object of the present publication. The authors performed rigorous clinical screening of patients with suspected Down syndrome followed by cytogenetic testing. Eleven of 71 (15.5%) patients with psychomotor delay and features of Down syndrome were found to have a normal karyotype. On subsequent fluorescent in situ hybridization (FISH) testing, only one of them had triplication of the Down syndrome region on FISH testing.

When neonates were analyzed separately, the false positive rate has improved up to 7.2%. Among publications where data on accuracy of Down syndrome diagnosis can be found there are some reporting on the prevalence of false positive diagnosis in neonates [Devlin & Morrison, 2004; Fried, 1980; Hall, 1964; Hindley & Medakkar, 2002; Melve et al., 2008; Sivakumar & Larkins, 2004]. The rate of false positives in our sample appeared to be the lowest, being closer to figure of 9.6% in Norway [Melve et al., 2008]. Annual rate of false positive diagnosis varied significantly, from 0% in 1990, 1995, and in 2000 to 21% (9 of 42) in 2001 (Figure 1). Obviously this variation did not depend on the clinical experience of the referring doctors. Similar figures were reported by Melve et al. [2008], the highest annual number of false positives in neonates was 18 (18.9%) and the lowest was 4 (4.8%).

False positive diagnosis implies a great undue mental stress for parents, therefore maximizing clinical diagnostic accuracy is of importance [Hindley & Medakkar, 2002]. Significance of expert clinical assessment of a patient before cytogenetic testing was explored by Sivakumar & Larkins [2004]. They reported a more favorable accuracy rate from Birmingham Women's Hospital (25 of 29 suspected cases had trisomy 21) compared to the West Midland region (false positive rate 14% and 36%, correspondingly). "This can be explained by the fact that the tertiary hospital may have more experienced neonatologists compared to the broad cohort of junior and senior pediatricians... We believe that an assessment by a senior pediatrician before testing may minimize the risk of negative results." [Sivakumar & Larkins, 2004]. The data from the present study, that is a low false positive rate as the result of expert clinical assessment by clinical geneticists, support this suggestion.

4.2 Degree of certainty about the diagnosis of Down syndrome

4.2.1 Degree of certainty about the diagnosis of Down syndrome in false positive cases

Despite the widely held belief that the clinical diagnosis of Down syndrome is very obvious, some publications report on difficulties of clinical judgment arising in the neonatal period [Druce et al., 1995; Fried, 1980; Hall, 1966; Hindley & Medakkar, 2002; Lee et al., 1961]. Factors which alter suspicion of Down syndrome are known to be early delivery and prematurity [Mikkelsen, 1988]. No data on sex difference in suspicion of Down syndrome or in degree of certainty of DS diagnosis were reported before.

Source	Country	Study period	Age of patients	Number of tested patients	Proportion of false positive diagnosis
Hamerton et al., 1965	UK	1960-1964	not specified	173	16 (9%)
Engel et al., 1970	Germany	1963-1968	various ages	365	6 (15%)
Johnson et al., 1985	Ohio, USA	1970-1981	various ages	769 ^a	48 (6%)
	New York, USA	1980-1983	various ages	126 ^b	10 (8%) ^c
Szollar et al., 1983	Hungary	1970-1979	under 1 yo	214	16 (7.5%)
			1 yo and older	85	3 (3.5%)
Czeizel, 1988	Hungary	1973-1982	various ages	81	4 (5%)
Baccichetti et al., 1990	Italy	1988	teenagers and adults predominantly	116	14 (12%)
Ballesta et al., 1997	Spain	not specified	not neonates	71	11 (15.5%) ^d
Ahmed et al., 2005	Pakistan	1998-2001	various ages	325	30 (9%) ^e

^{a,b} cytogenetic confirmation in about 77% of the patients; ^c including one case with trisomy 18; ^d FISH study of 11 cases detected a partial trisomy 21 in one case; ^e including 12 cases with other chromosomal anomalies

Table 5. Accuracy of the clinical diagnosis of Down syndrome in patients of various ages

Data presented in Table 2 suggests that the level of certainty in false positives cases was comparably low, decreasing with the patients' age. The diagnosis at clinical examination seemed obvious in 22% of neonates and in only 6% of children 1 year and older. However a proportion of clinical diagnosis suggestive of mosaicism increased with the patients' age, from 3% in neonates to about 10% in the oldest group of patients. Surprisingly, despite a strong prevalence of females among false positive children, a higher level of certainty of Down syndrome diagnosis was given to male patients (Table 3). In males, unquestionable Down syndrome or suspected mosaicism were indications for cytogenetic testing in 20% and in 8.5 % of the cases, while in females these figures were 14% and 4% respectively.

4.2.2 Degree of certainty about the diagnosis of Down syndrome in confirmed cases

The data reported above prompted the author to taking a quick look at degree of certainty of the clinical diagnosis in the cases of true Down syndrome. It was found that 17 of 106 (16%) neonates with Down syndrome born during 2007-2009 had a questionable clinical diagnosis (including one diagnose accompanied with three question marks), among them there were 8 males and 9 females. Thus, at least in neonates with Down syndrome, there was no association of clinical suspicion of the diagnosis with the gender of the patient.

Source	Geographic area	Study period	Number of tested patients	Proportion of false positive diagnosis
Hall, 1964	Sweden	1961-1962	43	5 (11.6%)
Fried, 1980	Israel	1973-1977	30	4 (13.3%)
Hidley, & Medakkar, 2002	UK	1999-2000	962	307 (32%) ^a
Devlin & Morrison, 2004	Northern Ireland	1969-2001	268 ^d	82 (31%) ^b
Sivakumar & Larkins, 2004	UK	2000-2002	233	85 (36%)
Melve et al., 2008	Norway	2001-2005	376	36 (9.6%)
Present study	Russia	1986-2009	1146	83 (7.2%) ^c

^a including one case with 49,XXXXY; ^b including 5 females with another chromosomal abnormality; ^c including 2 males and 6 females with another chromosomal abnormality; ^d neonates constitute 90% of the patients

Table 6. Accuracy of the clinical diagnosis of Down syndrome in neonates

4.3 Sex ratio in Down syndrome

4.3.1 Sex ratio in cases considered or proved to be true Down syndrome

Sex ratio in true Down syndrome is well known to be skewed towards males [Mikkelsen, 1988; Mutton et al., 1996]. Meta-analysis of publications reporting cytogenetic profile of Down syndrome worldwide [Kovaleva, 2002] showed typical male prevalence (SR ~1.3) among both patients with regular trisomy 21 and carriers of translocation trisomy 21, either sporadic or inherited. The only exception is mosaic variant of trisomy, where some prevalence of females was documented (SR~0.96).

Several hypotheses have been put forward to explain the skewed sex ratio in Down syndrome. Meiotic disturbance (non-homologous co-orientation in male meiosis) [Kovaleva, 1992; Petersen et al. 1993], fertilization event (greater accessibility of Y-bearing sperm to ova disomic for chromosome 21 or promotion of non-disjunction in the ova by Y-bearing sperm) [Ferguson-Smith & Yates, 1984; Kovaleva & Mutton, 2005], and post-fertilization events (intrauterine selection against females) [Huether et al., 1996; Hook et al., 1999] have been discussed. Data from recent studies supports suggestion that male excess among live born with non mosaic trisomy 21 might be due to selection against female fetuses [Oliver et al., 2009; Kovaleva, 2010]. Female prevalence among carriers of mosaic trisomy was suggested to be a result of sex-specific chromosome loss in early embryogenesis [Kovaleva, 2005].

The trigger of the present study was an observation of an intriguing dynamics of sex ratio in Down syndrome in St. Petersburg (former Leningrad) within period of 1970-1996 [Kovaleva et al., 1999] subsequently confirmed by the meta analysis of the literature [Kovaleva, 2002]. It was a steady increase in sex ratio from a population figure of 1.05 or even less in the earliest studies in 1940's to 1.3 - 1.6 in the studies conducted during late 1980's (Figure 2). Analysis showed that this increase was accounted for by the growing use of karyotyping to

confirm the diagnosis. Among individuals with a clinical diagnosis only, sex ratio was 0.97 (1160 males/1198 females) [Collman & Stoller, 1962; Davidenkova et al., 1965; Huether, 1990; Kovaleva et al., 2001; Staples et al., 1991] while among individuals with confirmed trisomy 21 this figure was 1.31 (1918 males/1466 females) [Huether, 1990; Kovaleva et al., 2001; Mikkelsen et al., 1976; Mikkelsen et al., 1990; Sharav, 1991; Staples et al., 1991; Stoll et al., 1990; Wahrman & Fried, 1970]. Correspondingly, in samples where proportion of clinical diagnosis only was 30% and more, intermediate figure of 1.12 (1950 males/1742 females) [Baird & Sadovnik, 1987; Christoderescu et al., 1977; Johnson et al., 1996; Kallen et al., 1996; Kovaleva et al., 2001; Staples et al., 1991] was observed. These observations raised a suggestion that low sex ratio in Down syndrome patients with clinical diagnosis only might be accounted by a large proportion of false positive diagnosis in females [Kovaleva, 2002].

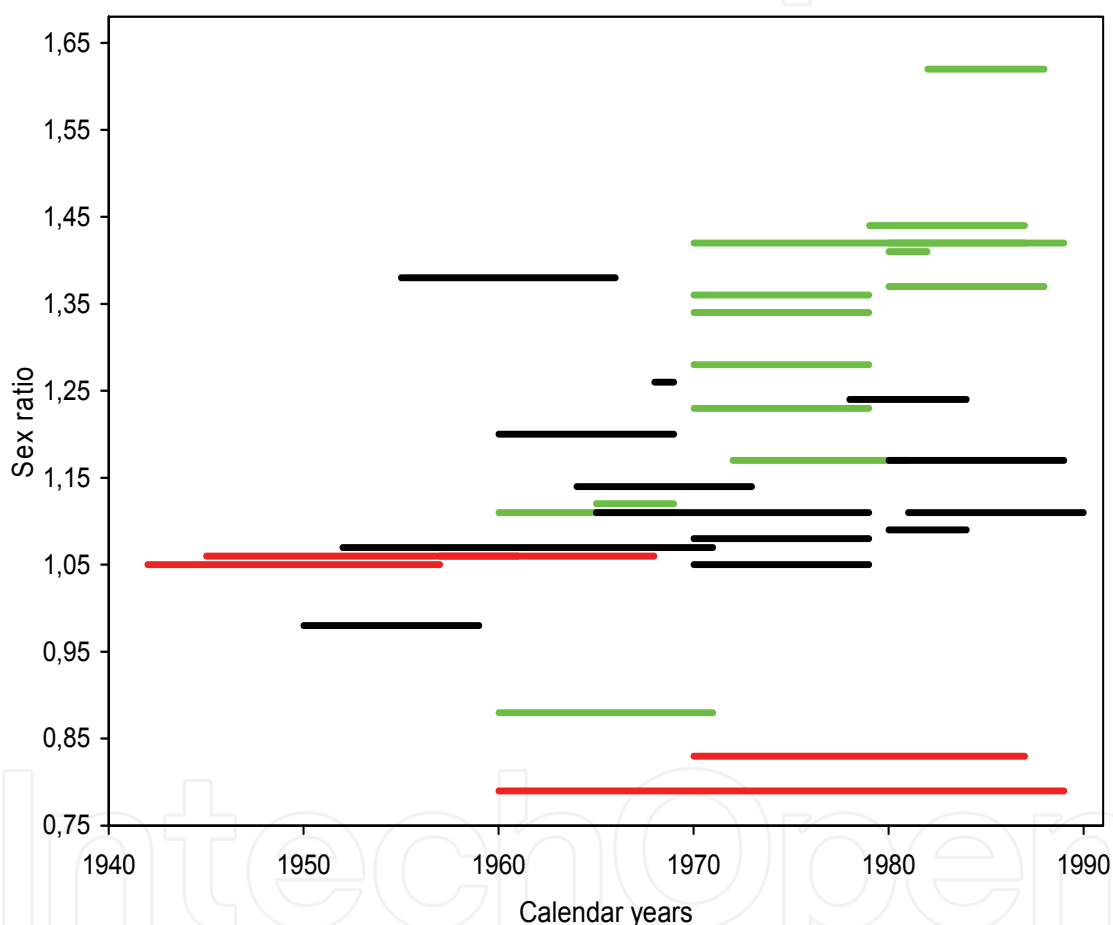


Fig. 2. Sex ratio in Down syndrome, data from epidemiological studies worldwide (adapted from Kovaleva [2002]). Red line: clinical diagnosis only; black line: clinical diagnosis or trisomy 21, green line: trisomy 21

4.3.2 Sex ratio in false positive diagnosis

Though theoretically, misdiagnosis should occur uniformly in both sexes, data from the present study demonstrates a significant female prevalence among false positive patients. In neonates, a five-fold prevalence of females over males was detected (17 males/86 females, SR = 0.20, different from population value of 1.06, $p < 0.0001$). Female excess diminished with older children; two-fold prevalence was found among children of the age up to 1 year

old (24 males/44 females, SR = 0.55, $p = 0.0052$), and notable but statistically insignificant prevalence among patients aged 1 year and older (29 males/35 females, SR = 0.83, $p > 0.05$). Therefore, data from the present study supports the suggestion of low sex ratio in Down syndrome patients with clinical diagnosis only as the result of a large proportion of false positive diagnosis in females. However the reason of female predominance among the clinically suspected Down syndrome remains unclear.

Patients with clinical features of Down syndrome but without trisomy 21 were reported occasionally before the advent of molecular technologies allowing definite detection of Down syndrome critical region located at chromosome 21 [Hall, 1961; Hamerton & Polani, 1962; Bowen et al., 1974]. As an explanation for absence of trisomy 21 in different tissues of patients with apparent manifestations of the syndrome, several suggestions were proposed: (1) low-level mosaicism, (2) the presence of the trisomic cell line in tissues other than those investigated, (3) elimination of the aberrant cell line *in vivo* or selective regress *in vitro* [Engel et al., 1970], and (4) gene mutation that might cause a "phenocopy" [Hall, 1962].

Subsequent studies showed the presence of a cryptic duplication of the Down syndrome critical region in individuals with clinical diagnosis of Down syndrome and an apparently normal karyotype [see for reference Forster-Gibson et al., 2001]. However several patients with mental retardation and Down syndrome phenotype, but without molecularly detectable duplication of the critical region, have been reported [McCormick et al., 1989; Ahlbom et al., 1996]. The majority of them were females. For example, a woman with clinically typical Down syndrome but apparently normal chromosomes, was extensively examined for the presence of any partial trisomy for any segment of chromosome 21. Since the proposita's parents were half-sibs, and her sister suffered from the same disorder as the proposita, the authors suggested an autosomal recessive disorder which is phenotypically indistinguishable from Down syndrome [Ahlbom et al., 1996]. As it was mentioned above, FISH testing of 11 patients with developmental delay and clinically obvious Down syndrome revealed only one of them who had triplication of the critical Down syndrome region. Unfortunately the gender of the patients was not reported [Ballesta et al., 1997].

The data obtained in the present study suggest that gender in particularly significantly affects clinical suspicion of Down syndrome in neonates. Since characteristic features allowing suspicion of Down syndrome include facial dysmorphisms, one may hypothesize sex differences in the normal process of facial cranium ontogenesis during perinatal period. In patients aged one year and older, sex ratio (0.83) appeared to be close to sex ratio typical to carriers of mosaic trisomy 21 (0.96). In this group, proportion of mothers of advanced age seemed to be increased which might support a suggestion of undetected mosaicism in some of these patients. An abnormal condition(s) specific to females might also be implicated in a proportion of the misdiagnosed cases.

4.4 Implications of false positive-female-prevalence-phenomenon to Down syndrome epidemiology

The observation of female prevalence in false positive clinically diagnosed cases allows an insight into the ground for reported sex ratio variability in Down syndrome. For example, the ECLAM (Estudio Colaborativo Latinoamericano de Malformaciones Congenitas) group reported as "an unusual finding" a markedly low sex ratio (0.98) found in 3,157 newborn Down syndrome patients in South America populations [Carothers et al., 2001]. Only 13% of the patients were reported to have confirmed diagnosis, therefore, in the light of the data

presented in this paper, a low sex ratio among patients mostly clinically diagnosed as Down syndrome, is a well expected finding.

Moreover, based on data on sex ratio in both all clinically diagnosed cases and true Down syndrome cases in a population where sufficient completeness of cytogenetic confirmation is not readily achievable, it is realizable to calculate a crude rate of false positives [Kovaleva, 2002]. For example, assuming all males among clinically diagnosed cases in ECLAM's sample to be true Down syndrome (which can not be absolutely correct since some false positive cases might be found among males) and typical for Down syndrome sex ratio to be 1.3, for 1563 males, 1203 females (not 1594) are expected, with odd number of 391 females. Resulted proportion of misdiagnosed cases is $391/3,157=12\%$.

The results from the present study might have some further implications. (1) Overestimation of maternal age-specific rates due to false positive cases, in young women predominantly, might take place in the early years of monitoring of Down syndrome, as well as in populations with a high proportion of unconfirmed cases (those covered by Chernobyl fallout in the Former Soviet Republics). (2) It was generally accepted that maternal age specific risks were stable over time, and variations in population rates were explained by changing in maternal age composition [Huether et al., 1998; Carothers et al., 2001]. However if age-specific rates stay stable over long time, irrespective of increase in proportion of confirmed cases, it might indicate an increase in real rates. (3) The results from this study would suggest that the use of epidemiological data collected on Down syndrome prior to routine cytogenetic analysis, should be reconsidered in meta-analyses of Down syndrome population data.

5. Conclusion

The present study is the largest study to address the accuracy of clinical diagnosis of Down syndrome and the first one demonstrating that gender may affect a clinical suspicion of a chromosomal disease. The advantages of this study are well-defined geographical population, clinical screening of the cases suspected to have a chromosomal disease by experienced clinical geneticists prior to requesting for cytogenetic testing, a high completeness of cytogenetic confirmation of the Down syndrome diagnosis, and perfect recording of the cases on logbooks of the cytogenetic laboratory at the St. Petersburg Centre for Medical Genetics. Apparent limitations of this study are a lack of detailed clinical description of the cases and absence of follow-up. Additional studies, both clinical and genetic, would be reasonable for uncovering mechanism(s) responsible for the remarkable sex bias in clinical suspicion of Down syndrome.

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This book provides a concise yet comprehensive source of current information on Down syndrome. Research workers, scientists, medical graduates and paediatricians will find it an excellent source for reference and review. This book focuses on exciting areas of research on prenatal diagnosis - Down syndrome screening after assisted reproduction techniques, noninvasive techniques, genetic counselling and ethical issues. Whilst aimed primarily at research worker on Down syndrome, we hope that the appeal of this book will extend beyond the narrow confines of academic interest and be of interest to a wider audience, especially parents and relatives of Down syndrome patients.

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