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Opinion

Neglected Phenomenon: Female Predominance in Clinically Diagnosed Down syndrome

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Abstract

A female prevalence among patients suspected clinically to have DS but without T21 (false-positive diagnose) was documented in a chapter titled "Gender affects clinical suspicion of Down syndrome" in 2011. Since then no further studies followed probably because such patients have routinely been taken for carriers of undetected mosaicism due to either its very low level or the presence in other tissues unavailable for cytogenetic testing. Current report is intended to explain the difference between the mentioned patient cohorts.

ABBREVIATIONS

T21: Trisomy of chromosome 21; AMA: Advanced Maternal Age; DS: Down Sydrome; SR: Sex Ratio

INTRODUCTION

Down Syndrome (DS) is one of the most common indications for cytogenetic testing. In most cases the clinical diagnosis is confirmed by the presence of an additional chromosome 21 (trisomy 21, T21). Three features have been established, a strong association of free trisomy 21 frequency with Advanced Maternal Age (AMA), a predominance of males among carriers of non mosaic T21, and a slight predominance of females among carriers of mosaic T21.

One more phenomenon, a female predominance among patients with clinical suspicion of DS but without T21was described in the chapter "Gender affects clinical suspicion of Down syndrome" in 2011 [1]. This chapter has been downloaded over 5,000 times, but no further research has been conducted on this topic. The most likely explanation is that such patients were commonly assumed to be carriers of undetected mosaicism either due to its very low level or due to its presence in other tissues inaccessible for cytogenetic testing.

It has been widely accepted that mosaicism occurs in a low proportion of T21 carriers, around 1-2% [2]. A more detailed analysis of data from large population-based studies (over 1000 DS patients diagnosed postnatally) revealed variation in this proportion, ranging from 0.8% in Egypt and 1% in Kuwait to 4.6% in Hungary [3-11]. Presumably, this variation can be explained by the required number of the cells evaluated. The average figure for over 28,000 patients is 2.3% of all free T21 carriers.

The average sex ratio (SR, male-to-female ratio) in these studies of 0.91 is consistent with the data from the National Down Syndrome Cytogenetic Register in England and Wales (NDSCR) [5] that in mosaic T21 the SR ratio is less than 1.0 as opposed to the ratio in non mosaic cases which is close to 1.2.

Some authors reported AMA rate in mosaic carriers to be higher compared to that in non mosaic patients [8, 9]. Later, Joan Morris, using data from the NDSCR, stated that the maternal age distribution in trisomy 21 with mosaicism differed from that in nonmosaic trisomy 21. Approximately two-thirds of trisomy 21 with mosaicism appeared to have the same age-related risks as nonmosaic trisomy 21, while one-third appeared to be independent of maternal age [12].

Summing up the above, one may conclude that the demographics of patients with clinical suspicion of DS but with normal karyotype, differ from those of patients with mosaicism. Their proportion among patients tested for

Table 1: Accuracy of the clinical diagnosis of Down syndrome in neonates *

Source	Geographic area	Study period	Number of tested patients	False-positive diagnoses	
				Proportion	Sex ratio
Hall, 1964	Sweden	1961-1962	43	5 (11.6%)	ns
Fried, 1980	Israel	1973-1977	30	4 (13.3%)	ns
Koroleva et al., 1994	Russia	1989-1993	45	20 (44%)	ns
Hidley & Medakkar, 2002	UK	1999-2000	962	307 (32%)	ns
Sivakumar & Larkins, 2004 *	UK	2000-2002	233	85 (36%)	ns
			29	25 (14%)	ns
Devlin & Morrison, 2004	Northern Ireland	1969-2001	268	82 (31%)	ns
Melve et al., 2008	Norway	2001-2005	376	36 (9.6%)	ns
Salomskiene et al., 2009	Lithuania	ns	134	43 (32.1%)	ns
Kovaleva, 2011	Russia	1986-2009	1146	83 (7.2%)	0.17
Zisovska et al., 2013	Macedonia	2008-2012	128	85 (66.4%)	0.42
Total			3394	693 (20. 4%)	0.30

Table 2: Accuracy of the clinical diagnosis of Down syndrome in patients of various ages *

Source	Geographic area	Study period	Number of tested patients	False-positive diagnoses	
				Proportion	Sex ratio
Hamerton et al., 1965	UK	1960-1964	173	16 (9%)	ns
Engel et al., 1970	Germany	1963-1968	365	52 (15%)	ns
Johnson et al., 1985	Ohio, USA	1970-1981	769	48 (6%)	ns
	New York, USA	1980-1983	126	10 (8%)	ns
Szolar et al., 1983	Hungary	1970-1979	214 < 1 yo	16 (7.5 %)	ns
			85 ≥ 1 yo	3 (3.5%)	ns
Czeizel, 1988	Hungary	1973-1982	81	4 (5%)	ns
Cortes et al., 1990	Chile	1977-1989	201	22 (12%)	ns
Baccichetti et al., 1990	Italy	1988	120	14 (11.7%)	ns
Ballesta et al., 1997	Spain	ns	71	11 (15.5%)	ns
Butler, Hamill, 1995	USA	1985-1992	251	113 (45%)	0.47
Ahmed et al., 2005	Pakistan	1998-2001	325	30 (9%)	ns
Salomskiene et al., 2009	Lithuania	ns	393	19 (4.8%)	ns
Garduno-Zarazua et al., 2013	Mexica	1986-2010	581	71 (12%)	ns
Thillainathan et al., 2014	Sri Lanka	2006-2011	763	98 (13%)	ns
Flores-Ramirez et al., 2015; personal communication	Mexica	1992-2011	1921	96 (5%)	0.6
Polipalli et al., 2016	India	2010-2015	357	55 (15%)	0.77
Pande et al., 2017; personal communication	India	2015-2016	714	57 (8%)	0.68
De Baron et al., 2023	Peru	2017-2019	436	3 (0.7%)	ns
Akalin et al., 2024	Turkey	2013-2020	467	192 (41%)	0.59
Total			8240	914 (11%)	0.51

* Updated from [1]

T21 is significantly higher than that of patients with T21 mosaicism, and the prevalence of females is higher as well (Tables 1 and 2). Furthermore, according to Kovaleva [1], the proportion of AMA among false positive neonates is 7.5% which is not different from the general population (6% to 9% per year) suggests that this clinical essence is not age-dependent unlike to mosaicism carriers.

Unfortunately, neither detailed clinical description of false-positive patients nor follow-up studies have been conducted. The author hopes to draw attention to this phenomenon and uncover its genetic basis.

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