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Article *in* Journal of Clinical and Experimental Neuropsychology · December 2005

DOI: 10.1080/13803390490919119 · Source: PubMed

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Increased prevalences of left-handedness and left-eye sighting dominance in individuals with Williams-Beuren syndrome

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Handedness and eye sighting dominance were assessed in a sample of 50 individuals (25 male, 25 female; aged 5 – 38 years) with Williams-Beuren syndrome (WBS). The prevalences of left-handedness and left-eyedness were compared to the normative prevalences in the general population. We found significantly higher prevalences of left-handedness and left-eyedness in the WBS sample. The higher prevalences were more salient in younger than in older individuals and in male than in female individuals. We suggest that the increased prevalence of left-handedness in WBS is a consequence of a slower maturation rate, which allows deviation from a predetermined laterality pattern.
Keywords: Hand preference; Eyedness; Laterality; Development

Subjects with Williams-Beuren Syndrome (WBS) exhibit a distinctive profile of medical, cognitive, and neuroanatomical characteristics (Bellugi, Lichtenberger, Mills, Galaburda, & Korenberg, 1999). WBS is a rare, genetically based condition resulting from a hemizygous deletion of about 15 genes on chromosome band 7q11.23, including the gene encoding elastin, a protein that furthers tissue elasticity. Medical characteristics of the syndrome include cardiovascular anomalies, hypersensitivity to sounds, and distinctive facial features.

At an anatomical level, subjects with WBS display smaller brain volumes than normal controls, with a relative preservation of cerebral gray matter and a disproportionate reduction in cerebral white matter. However, the right occipital cortex shows an excess volume loss of gray matter. Other anomalies include a greater ratio of frontal to posterior cerebral lobe tissue and a proportionally larger superior temporal gyrus (Reiss et al., 2000). In addition, individuals with WBS show a reduced corpus callosum size that is most pronounced in the area of the splenium and isthmus (Schmitt, Eliez, Warsofsky, Bellugi, & Reiss, 2001).

The cognitive profile of individuals with WBS is characterized by low full scale IQ scores (average IQ = 55, range = 40 - 90), with relative strengths in expressive language, musical abilities and face processing and profound weaknesses in spatial cognition and visuomotor abilities (Bellugi et al., 1999). The pattern of linguistic strength and spatial cognitive deficits could be suggestive of right-hemisphere malfunction. However, as Bellugi, Wang and Jernigan (1994) have noted, subjects with WBS demonstrate preservation of several specific right hemisphere functions, such as face processing, semantic clustering, and recognizing affective prosody. Rather than being a hemisphere-specific pattern of deficits, it is more probable that the spatial cognitive inadequacies of WBS people are a consequence of cortical anomalies along the rostral-caudal axis, although other factors such as poor saccadic control may also be involved (van der Geest et al., 2004).

A further consequence of anomalous brain anatomy in WBS could be a greater prevalence of left-handedness. In clinical groups with evidence of mental retardation as a consequence of disturbed brain development (such as Down's syndrome, epilepsy, and autism), the prevalence of left-handedness is significantly raised (Lewin, Kohen, & Mathew, 1993). Bellugi et al. (1988) have described several cases that may be suggestive of greater prevalence of left-handedness in individuals with WBS, but to the best of our knowledge, there is no unequivocal empirical evidence that in WBS the prevalence of left-handedness is also raised. In the present study, we assessed the side biases in a relatively large sample of 50 individuals with WBS.

The explanation of the greater prevalence of left-handedness in clinical subgroups remains unclear. There are numerous theories about the biological and cultural origins of (non)right-handedness (for review, see Van Strien, 2000). Models of genetic and intra-uterine determinants of handedness are the most likely prospects, but cannot easily explain the raised prevalence in clinical groups, because they are typically concerned with the 10-12% left-handers in the general population. The pathological left-handedness (PLH) model of Satz, Orsini, Saslow & Henry (1985) postulates that left-handedness is determined either genetically (resulting in natural left-handedness) or pathologically (resulting in PLH). In their view, PLH is the consequence of early brain injury, more specifically, a predominantly left-sided hemispheric lesion in the frontotemporal/frontoparietal areas, which onsets before the age of six. Satz et al. (1985) have provided clinical evidence for the PLH syndrome, which is characterized by impaired visuospatial abilities, relatively intact verbal abilities, right hemihypoplasia, and an altered pattern of speech lateralization. The PLH model can explain the increased rate of left-handedness in a sample of epileptic patients, but is less likely to apply to samples of individuals without focal brain lesions, such as individuals with Down's syndrome or with autism (Lewin et al., 1993). A possible explanation for the greater prevalence of

left-handedness in clinical subgroups without focal brain damage is that neurodevelopmental disorders are the consequence of developmental imprecision, that is, the inability of organisms to realize their exact developmental design because of additional genetic and epigenetic influences and developmental stresses. Left-handedness, although not an neurodevelopmental disorder itself, appears to be related to an increased incidence of markers of developmental imprecision (Gangestad & Yeo, 1997). Thus, handedness may reflect variations in susceptibility to neurodevelopmental disorders.

In daily life, someone is considered right-handed if he or she uses the right hand for writing. For research purposes, handedness can be determined by asking people (usually by means of a questionnaire) which hand they use for a number of activities. Questions concern actions like writing, grasping a tennis racket, cutting with a knife, and throwing a ball. Handedness questionnaires are both reliable and valid (Bryden, 1987): repeated testing of a subject results in the same score and the agreement between the indicated hand preference on a certain item and the actual execution of an activity is very high. Also, the intercorrelations between the items of preference questionnaires are generally very high, which indicates that they measure a unifactorial trait (Van Strien, 1992, 2003). In the general population, the scores on a handedness questionnaire result in a J-shaped distribution with a small peak of extremely left-handed individuals , ambidexter individuals in the middle, and a large peak of extremely right-handed individuals.

In the present sample of participants with WBS, handedness was ascertained by means of a direct assessment procedure (i.e. actual performance) based on 10 items from a handedness questionnaire (see method). The WBS group comprised both children and adults. The prevalence of left-handedness in this clinical group was compared to the prevalence of left-handedness in the general population. A large survey of the general Dutch population (performed by the Dutch Central Statistical Office, CBS, 1986) allowed us to determine the normative prevalence of left-handedness in subgroups of male and female children and adults.

In addition, the eye preferences of individuals with WBS were determined. Eye preference (sighting dominance) refers to activities in which one eye is preferentially used to view through for instance a keyhole or magnifying glass. This preference appears to be independent of monocular visual acuity (Pointer, 2001). There are no Dutch norms for eye preference, but a meta-analysis of the relationship between handedness and eyedness in more than 54,000 subjects (Bourassa, McManus, & Bryden, 1996) provides data that can be used for comparison. Bourassa et al. found that the normative prevalence of left-eyedness equalled 36.5%. From their data the hand-eye concordance (i.e. left-handedness in combination with left–eyedness or right-handedness in combination with right-eyedness) can be estimated for the general population (concordance = 64.8%). The prevalence of left-eyedness and the hand-eye concordance in our WBS sample will be compared with these numbers.

Method

Participants

Fifty individuals (25 males, 25 females) with WBS were tested for handedness and eye preference. Their ages ranged from 5 years and 10 months to 38 years and 3 months, with

a mean age of 17.34 years. When the sample was split as a function of age, ages ranged from 5 to 15 years four the group of younger participants (n = 25, M = 10.4, SD = 2.95, mode = 10) and from 16 to 38 years for the group of older participants (n = 25, M = 24.64, SD = 6.48, mode = 20). Mental ages were assessed by means of the WPPSI/WISC Vocabulary and Block Design subtests and ranged from 3 years and 0 months to 9 years and 10 months (M = 5.66, SD = 1.32). All participants were phenotypically and genetically screened for WBS. For all of them, the diagnosis of WBS was genetically confirmed using fluorescent in situ hybridization (FISH) to test for the deletion of genes (among which ELN and CYLN2) in the 7q11.23 region on chromosome 7. The study was approved by the ethics committee of the Erasmus Medical Center. Informed consent for participation in this study was given by either the parents of the participants or the participants themselves.

Laterality Measures

All participants were tested individually. Handedness was assessed by a procedure based on the 10 items of the Dutch Handedness Questionnaire (Van Strien, 1992, 2003). The items concerned the following activities: drawing, using toothbrush, twist off screw cap of a bottle, throwing ball, using hammer, using tennis racket, using scissors, stirring, using eraser, and using pencil sharpener. Instead of filling out the questionnaire, the participants were asked to demonstrate which hand they would use for a particular activity. They were given the actual objects (e.g., ball, hammer, eraser). In general, performance was satisfactory. For drawing, we asked the participants to copy simple figures. The quality of these copies was very low, but the hand preference could clearly be observed. Eye preference was assessed by having the participants look through a small hole in a black card, a small tube, a kaleidoscope, and a magnifying glass.

Scoring

Handedness scores could range from –10 (left hand preference for all activities) to 10 (right hand preference for all activities). Participants were classified as strongly left-handed (LL, handedness scores between –10 and –8), weakly left-handed (L, scores between –7 and –4), ambidexter (A, scores between –3 and 3), weakly right-handed (R, scores between 4 and 7), or strongly right-handed (RR, scores between 8 and 10). To measure handedness as a dichotomous variable, right-handedness was defined as having a R or RR score, while left-handedness was defined as having a LL, L, or A score. Previous research with 179 healthy, self-assessed right-handers demonstrated that none of them had a score lower than +4 on the handedness questionnaire (Van Strien, 1992, 2003), that is, all self-assessed right-handers fell in the RR and R categories.

Eye preference scores could range from strong left-eye preference to strong right-eye preference (LL – left eye for all four items; L – left eye for three items, NP - no preference, R – right eye for three items, RR – right eye for all four items). To measure eyedness prevalences in the WBS sample, right-eyedness was defined as having a R or RR score, while left-eyedness was defined as having a LL, L, or NP score.

Data Analysis
The exact binomial test was used to determine whether the observed prevalences of left-handedness and left-eyedness in the WBS sample exceeded the previously reported prevalences in the general population.

Results

Handedness
The distribution of the five handedness categories across the total sample of 50 individuals with WBS is shown in Figure 1. In this sample, the prevalence of left-handedness (LL, L, and A) was much higher (26.0%) than in the same age group (6 – 38 years) of the general population (expected frequency = 11.6%, see CBS, 1986, p = .004). In Table 1, the sample is split as a function of age and sex. From this table, it can be seen that the highest proportion of left-handed individuals was found in the group of young men with WBS. In the group of adult women with WBS, the prevalence of left-handedness was not different from the general population.

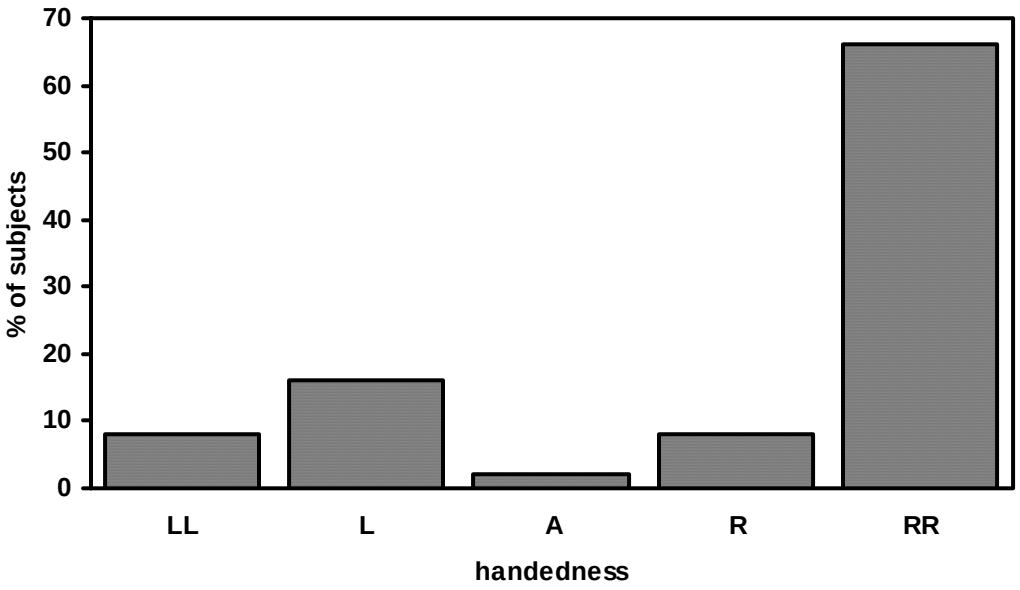

Figure 1. Distribution of the five handedness groups in the sample of individuals with the Williams-Beuren syndrome (LL = strongly left-handed; L = weakly left-handed; A = ambidexter; R = weakly right-handed; RR = strongly right-handed).

TABLE 1
Proportion of left-handers in the various groups of individuals with Williams-Beuren syndrome. P-values (binomial tests, exact significances, one-tailed) indicate the chance of observing the found proportion of left-handedness or higher given the expected frequency.

individuals with WBS	Number of left-handers	Expected frequency	Binomial test
5 - 15 years			
Male	4 out of 10 (40.0%)	14.7%	P = .037
Female	4 out of 15 (26.7%)	11.2%	P = .078
total	8 out of 25 (32.0%)	12.5%	P = .009
16 –38 years			
Male	4 out of 15 (26.7%)	11.9%	P = .094
Female	1 out of 10 (10.0%)	10.5%	P = .717
total	5 out of 25 (20.0%)	11.3%	P = .145
Male (all ages)	8 out of 25 (32.0%)	12.4%	P = .009
Female (all ages)	5 out of 25 (20.0%)	10.7%	P = .122
total sample	13 out of 50 (26.0%)	11.6%	P = .004

Eye Preference

The distribution of the five eye-preference categories across the total sample of 50 individuals with WBS is shown in Figure 2. The prevalence of left-eyedness was significantly higher (26 out of 50 = 52.0%) than the estimate for the general population (expected frequency = 36.5%, see Bourassa et al., 1996, p=.027).

When we split our participants according to handedness, we found that of the right-handed individuals with WBS, 45.9% exhibited a left eye preference (8 out of 17 men, 9 out of 20 women). This prevalence was higher than in right-handers in a normative population, but the difference only approached statistical significance (expected frequency = 34.4%; p = .098). Of the left-handed individuals with WBS, 69.2% exhibited a left-eye preference (5 out of 8 men, 4 out of 5 women). This prevalence was not different from the prevalence in left-handers in a normative population (expected frequency = 57.1%; p = .277).

The hand-eye concordance in the WBS sample equaled 58.0%. This concordance was not significantly lower than in the general population (normative concordance = 64.8%, p=.207).

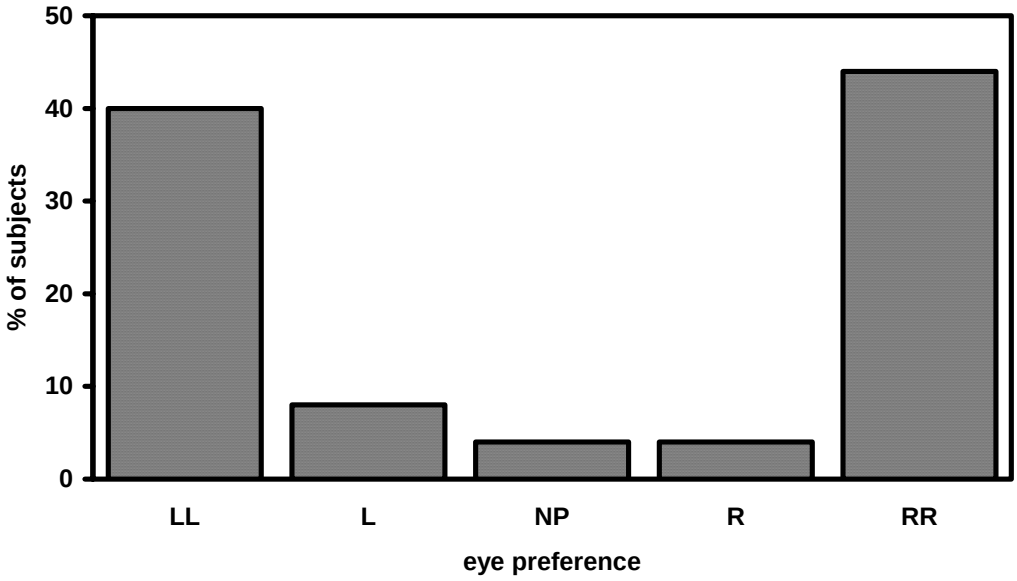

Figure 2. Distribution of eye-preference in the sample of individuals with the Williams-Beuren syndrome (LL = strongly left-eyed; L = weakly left-eyed; NP = no preference; R = weakly right-eyed; RR = strongly right-eyed).

Discussion

In the present sample of individuals with WBS, the prevalence of left-handedness was significantly higher than in the general population. Inspection of figure 1 reveals that the left-handers' scores did not fit the J-shaped distribution that is generally found in the general population. In the WBS sample there were twice as much L as LL individuals, whereas in the general population, much more LL than L individuals can be expected. For instance, Van Strien (1992) found a proportion of 81.6% LL in a sample of 245 healthy left-handed students. Although the present distribution is based on a small number of left-handers, it appears that the higher prevalence of left-handedness in the WBS sample is accompanied by a less extreme preference.

The increased prevalence of left-handedness in WBS most probably cannot be a direct consequence of the hemizygous deletion of genes in the 7q11.23 region, since other clinical groups with mental handicaps show a similar increase. However, it could be the outcome of a slower maturation rate. There is consistent evidence that, in the general population, delayed rates of maturation are associated with left-handedness. Compared to right-handers, left-handers have somewhat smaller body size in terms of both height and weight (Coren & Halpern, 1991), and more often report low birth weight (Van Strien, Bouma, & Bakker, 1987). In addition, left-handedness has also been connected to pubertal delay (Coren, Searleman, & Porac, 1986). In a longitudinal study comparing the physical growth and psychological development of short normal children with that of average height controls, short children had a lower birth weight, delayed bone age, and scored less well on tests of cognitive ability (Mulligan, Stratford, Bailey, McCaughey, &

Betts, 2001). Interestingly, 25% of these short normal children were left-handed. Mulligan et al. hypothesized that the hormones responsible for growth and development also are involved in brain laterality and cognitive development. From a developmental imprecision point of view, it is conceivable that right-handedness is the preset outcome of a normal neurological development. The more this development is slowed (e.g. by hormonal or epigenetic influences), the less the preset outcome (i.e. right-handedness) is likely, and the more often there will be random dominance (i.e. increased prevalence of left-handedness, see for similar conceptions, Coren & Halpern, 1991; Geschwind & Galaburda, 1987).

In WBS, there is a marked prenatal growth delay and adult height is approximately 10 cm below average (Partsch et al., 1999). So it may well be that the increased prevalence of left-handedness in WBS is not a consequence of this syndrome itself, but a consequence of a more general maturational lag, which is also present in other groups with mental handicaps such as Down's syndrome (Myrelid, Gustafsson, Ollars, & Anneren, 2002) and Prader-Willi syndrome (Hoybye, 2004). In autism however, neuroanatomical abnormalities are not accompanied by a more general (physical) maturational lag, as autistic children usually do not differ in height from controls or even show a generalized increased growth rate (e.g., Davidovitch, Patterson, & Gartside, 1996). The exact nature and extent of the interrelationships between handedness, maturational lag, and mental retardation therefore remain uncertain.

In the present study, the actual numbers of left-handed participants in the different subsamples are too small to warrant firm conclusions about the effects of sex and age. Yet, it is noteworthy that the highest prevalence of left-handedness (4 out of 10; 40%) was found in the group of 5 –15 years old boys with WBS. In the group of 16 – 38 years old women with WBS, the prevalence of left-handedness (1 out of 10; 10%) was comparable with the prevalence in the general population. The subtotals in Table 1 illustrate that significantly raised prevalences were found for younger but not for older WBS individuals, and for male but not for female WBS individuals.

Regarding the differential statistical results for the younger and older group, we can only conjecture that if the increased prevalence of left-handednes in WBS children were a consequence of a maturational lag, some of the youngest individuals classified as weak left-handers might be classified as right-handers at an older age. In the general population, definite hand preference is established around the end of age five in most children, but this could come about later in the WBS group. Whether such handedness shifts occur in young WBS children remains to be investigated.

There is consistent evidence that, in the general population, men have a greater chance than women to be left-handed (CBS, 1986; Harris, 1990). From Table 1 it can be seen that the prevalence of left-handedness among men with WBS is significantly higher than among men from the general population. Among women the effect of WBS on handedness is less noticeable. Various models have offered an explanation for the sex difference in handedness (Van Strien, 2000). According to a cultural explanation, women are more apt than men to give in to social pressure against left-handedness (see Harris, 1990). McManus and Bryden (1992) have offered a genetic explanation. They proposed a recessive, X-linked modifier gene that inhibits a hypothetical D-allele (*dextral*), which supposedly codes for right-handedness. There is no apriori reason why a sex-linked recessive gene would be more frequent in boys with WBS than in boys from the general

population. In our view, it may be more plausible that sex differences in handedness are the result of a slower maturation rate in boys compared to girls (e.g., Tanner, 1990), the effect being more pronounced in boys with WBS.

The prevalence of left-eyedness was significantly higher in the WBS sample than in the general population. Right-handers with WBS tended to exhibit a greater prevalence of left-eyedness while left-handers with WBS did not show a significantly raised prevalence. As Figure 2 shows, most participants (84%) exhibited strong eye preference (either LL or RR). This is in agreement with an unpublished study in which we found that 78% of a sample of 449 healthy left-and right-handed students had a strong eye-preference.

Across all participants, the hand-eye concordance was not different from the hand-eye concordance in the general population. The nature of the association between handedness and eyedness cannot readily be explained (Bourassa et al., 1996). It has been suggested that crossed dominance (i.e., left-handedness in combination with right–eyedness or right-handedness in combination with left-eyedness) is indicative of neurodevelopmental abnormalities. In right-handed schizophrenic patients, crossed dominance was associated with earlier clinical onset and smaller brain size (Tabares Seisdedos, Sanjuan Arias, Gomez-Beneyto, & Leal Cercos, 1999). In a sample of individuals with mental handicaps however, the prevalence of crossed dominance was similar to the prevalence found in the general population (Robison, Block, Boudreaux, & Flora, 1999). In the present WBS sample, no substantial evidence for a raised prevalence of crossed dominance was found either (although the right-handed individuals with WBS tended to exhibit a greater prevalence of left-eyedness and hence less concordance).

In summary, our data revealed significantly higher prevalences of left-handedness and left-eyedness in a sample of individuals with WBS, compared with the general population. For this reason, the empirical evidence that the prevalence of left-handedness is raised in various groups with mental handicaps can be broadened to include the group with WBS. The outcome for the present WBS sample suggests that increased left-side biases are a consequence of a slower maturation rate, which allows deviation from a predetermined laterality pattern.

Acknowledgements

The authors are grateful to the patients with Williams-Beuren Syndrome and their families for participating in this study. M.A. Frens was supported by NWO-VIDI. J.N. van der Geest was supported by grants from NWO (903-68-394) and the Revolving Fund of the Erasmus MC.

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