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Handedness Score in Unexplained Infertility, a Contribution to the Debate on Neuronal Function in Fertility

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Abstract

Aim: The aim of this study was to assess the value of handedness score as an indicator of neuronal function in predicting unexplained infertility (UI).

Methods: Fifty female patients with UI, 50 male patients with UI, 50 fertile female controls and 50 fertile male controls were evaluated in terms of handedness score obtained by using Edinburgh Handedness Inventory. Association between the score and the UI cases was assessed.

Results: Mean age of the female study population was 27.1 ± 3.4 years. Groups were comparable in terms of left/right handedness (12/38 vs. 15/35, p = 0.499). However comparison of mean handedness scores between the groups revealed a significant difference (64.6 vs. 74.2, p < 0.001). Handedness score was a significant predictor of UI among women patients (AUC = 0.749, p < 0.001). Optimal cut off value was obtained at a level of 72.5 with 80% sensitivity and 60% specificity. On the other hand, fertile and infertile male groups were comparable regarding left/right handedness (9/41 vs. 14/36 p = 0.235). Comparison of scores between groups revealed similar results (72.4 vs. 71.2, p = 0.663).

Conclusion: After screening for all the fertility diagnostic tests, handedness score that indirectly show the neuronal cascade function associated with the fertility problems may be used to confirm real UI in women.

Keywords

Handedness score, Neuronal function, Unexplained infertility

Introduction

An estimated 15% of couples remain childless after one year of unprotected intercourse, which represents approximately 140 million people worldwide [1,2]. Despite proper diagnostic work-up and as our knowledge of the events involved in normal conception is still limited, we fail to determine the cause of infertility in nearly half of these cases [3]. Sometimes abnormalities are likely to be present, but are not detected by conventional approaches.

The menstrual cycle is characterized by a complex combination of synchronized endocrine events that the hypothalamus, the anterior pituitary and the ovaries are all play roles for its regularity [4]. This complex combination is necessary for successful oocyte development, ovulation, fertilization and implantation. In fact it is also thought that in addition to this complex combination reproductive neuroendocrinology is the real indicator of the infertility [4,5].

Although the etiology of handedness is unclear, it is thought to be a reflection of variety in the integrity of the brain microstructure that indirectly shows the nervous system function [6-8]. Some people are pure right handed, some are pure left handed, whereas, some are not pure in handedness, eventually a scoring system was developed to determine the handedness of a person [9].

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Neuronal innervations of the ovaries include sympathetic, parasympathetic and sensorial components of the autonomic nervous system, and come to the ovary through the ovarian plexus, the superior ovarian nerve (SON), and the vagus nerve [10-12]. This nerves discharge a series of neurotransmitters from its endings to the interior of the gland; some of which have been considered regulators of steroidogenesis, early follicular development and ovulation [13-15]. As an indicator of lateralization handedness can show the diversity of central nervous system and autonomic nervous system. Because handedness can be effortlessly ascertained, it has potential of being used as a clinical marker of increased risk if the associations are meaningful and hold over time. Recently, it has also been suggested that non-right handedness, particularly mixed-handedness, is associated with a number of medical conditions [16].

In this study, we used handedness score to determine the degree of handedness and assessed this score, as an indirect indicator for nervous system function, whether it is predictive for real unexplained infertility (UI) cases.

Material and Methods

In this case control study, 50 female patients with UI, 50 male patients with unexplained male infertility, 50 fertile female patients and 50 fertile male patients were evaluated in Zekai Tahir Burak Women's Health Research and Education Hospital from March 2013 to August 2013. Informed consent was obtained from each participant. The study was approved by the Local Ethics Committee (2013/24-02) and conducted in accordance with the ethical principles described by the Declaration of Helsinki. Inclusion criteria for unexplained female infertile group were: women with infertility lasting more than 1 year, age more than 23 and less than 35 years, body mass index (BMI) > 19 kg/m^2 and < 30 kg/m^2, normal cycles, at least one open tube in hysterosalpingography (HSG), normal male factor, documentation of ovulation with midluteal serum progesterone levels exceeding 5 ng/mL, normal hormonal profile (thyroid stimulating hormone (TSH), prolactin (PRL), testosterone, and dehydroepiandrosterone sulfate), and day 3 follicle stimulating hormone (FSH) ≤ 12 IU/L. UI was diagnosed based on a normal semen analysis according to World Health Organization criteria [17].

On the other hand the patients were excluded if they have experienced assisted reproductive technology (ART) procedures, cervicitis, age more than 35 and BMI > 30. There was no history of underlying disease and surgery; moreover HSG did not detect any abnormality. Additionally, to rule out the male factor the semen of husband of all patients were analyzed and did not show any abnormality. The criterion for inclusion in the unexplained male infertile group was infertility, as judged by abnormal semen parameters on at least two separate analyses, with sperm parameters below the cutoff levels defined by the World Health Organization [17]. Exclusion criteria included Y chromosome microdeletions or karyotype abnormalities, genital trauma or testicular torsion, a testicular volume of less than 10 ml, cryptorchidism, varicocele, and the use of immunosuppressant or cytotoxic drugs. Semen specimens were collected by masturbation into a sterile plastic container after at least 3 days of sexual abstinence. All the men voluntarily signed the informed consent for molecular analysis of their blood samples. Control groups were fertile male and female individuals who had at least one child. Hand preference was determined using the Edinburg Handedness Inventory (EHI) to quantify the degree of hand preference in both right- and left-handers and showed that the greater the degree of handedness the greater the lateralized difference in motor cortex activation during use of the dominant hand. The EHI was first published in 1971 by R.C. Oldfield and has been used in various scientific studies as well as popular literature [9]. The questionnaire serves as self-report measure of hand preference, as participants were asked to indicate their preferred hand for 15-unimanual tasks. Each question permits two responses: "left hand" or "right hand". Subjects with handedness scores less than zero were considered as left-handed, subjects with scores greater than zero were considered as right-handed. Degrees of Handedness calculated on the basis of laterality questions (LQs) computed from the EHI as: (Right - Left)/(Right + Left) × 100. The questionnaire evaluates handedness values from - 100 for extreme left hand use to + 100 for extreme right hand use. (-) value refers only to the left hand and are not taken into account in arithmetic calculations.

Statistical Analysis

The Statistical Package for Social Sciences software (SPSS) version 22.0 (Chicago, IL, USA) was used for further statistical evaluation as required. Where appropriate, differences in demographic and clinical data were assessed using parametric (student's t-test) and non-parametric (Mann-Whitney U) tests. Receiver operating characteristic (ROC) analysis of the area under the curve (AUC) was used to determine the predictive values of handedness score for UI in both sex. Pearson correlation analysis was used for the determination of correlations between handedness score and other hormonal and demographic variables. For categorical measures, χ^2 tests were applied. For each test statistic, a probability value of $P < 0.05$ was regarded as significant.

Results

Mean age of the female study population was 27.1 years (23-34), there were 27 subjects with left handed, 73 subjects were right handed. No significant differences were observed between the 2 groups in terms of age and BMI. The mean infertility duration was 34.2 ± 8.2 months among infertile women. Infertile and fertile women were comparable in terms of left/right handedness (12/38 vs. 15/35, p = 0.499). Mean handedness

Table 1: Characteristics of the unexplained infertile female group and control group with respect to handedness scores.

	Women with unexplained infertility (n: 50)	Fertile female control group (n: 50)	P value
Age (years)	27.0 ± 3.3	27.2 ± 3.5	0.758
Hand dominance			0.499
Left	12 (24)	15 (30)	
Right	38 (76)	35 (70)	
Handedness score			
Left (-)*	64.7 ± 13.2 (32-93)	78.1 ± 19.3 (23-92)	< 0.001
Right	64.5 ± 14.8 (45-93)	72.5 ± 18.5 (21-92)	< 0.001
Total	64.6 ± 14.4 (32-93)	74.2 ± 18.7 (21-92)	< 0.001
BMI (kg/m^2)	23.7 ± 3.2	24.2 ± 3.1	0.480
FSH (U/L)	6.7 ± 1.2	7.1 ± 1.2	0.110
Estradiol (pg/mL)	42.4 ± 11.4	35.8 ± 10.8	0.001
LH (U/L)	6.8 ± 1.3	6.7 ± 1.2	0.748
PRL (ng/mL)	16.8 ± 5.1	16.1 ± 4.8	0.485
TSH (U/L)	2.1 ± 0.6	2.2 ± 0.7	0.884

*(-) symbol was solely used to indicate the left dominant hand. BMI: Body mass index; FSH: Follicle stimulating hormone, LH: Lutenizing hormone; PRL: Prolactin; TSH: Thyroid stimulating hormone. Data are expressed as mean ± standard deviation, minimum maximum, and number (percentage). A P value < 0.05 is considered statistically significant.

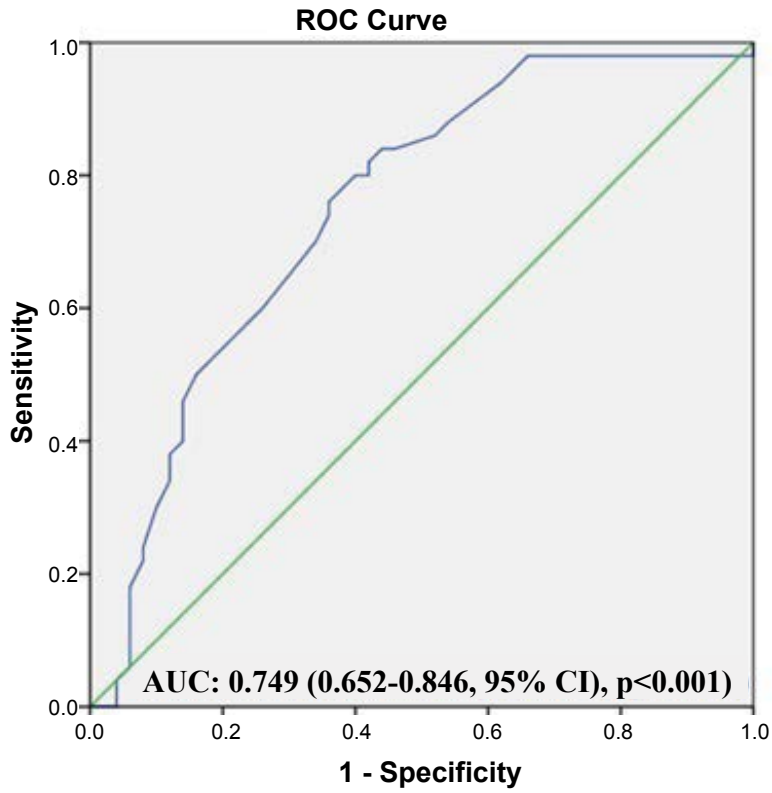

Figure 1: ROC curve of handedness score to predict women with unexplained infertility.

score was 69.4 (21-93). However, comparison of mean handedness scores between groups revealed a significant difference (64.6 vs. 74.2, p < 0.001). Baseline hormone levels were similar in both groups with the exception of estradiol levels. All data belong to women subjects were summarized in Table 1. Handedness score was a significant predictor for the unexplained infertile women according to the ROC curve analyses [AUC: 0.749 (0.652-0.846, 95% CI), p < 0.001) (Figure 1)]. Optimal cut off value was obtained at a level of 72.5 with 80% sensitivity and 60% specificity.

Mean age of the male study population was 27.2 years (23-34), there were 23 subjects with left handed, 77 subjects were right handed, fertile and infertile groups were comparable in terms of left/right handedness (9/50 vs. 14/50 p = 0.235). Comparison of mean handedness scores between groups revealed similar results (72.4 vs. 71.2 p = 0.663) (Table 2). Mean serum total testosterone levels of infertile males were 441.4 ± 141.4 ng/dL. The other hormone levels including FSH, Luteinizing hormone (LH), PRL, TSH were 3.8 ± 1.7 U/L, 4.2 ± 4.0 U/L, 12.8 ± 4.5 ng/mL, 2.0 ± 0.7 U/L, respec-

Table 2: Characteristics of the unexplained infertile male group and control group with respect to handedness scores.

	Males with unexplained infertility (n:50)	Fertile male control group (n:50)	P value
Age (years)	27.1 ± 4.2	27.2 ± 4.3	0.880
Hand dominance			
Left	14 (24)	9 (30)	0.235
Right	36 (76)	41 (70)	
Handedness score			
Left (-)*	67.9 ± 15.4 (32-93)	68.0 ± 15.9 (38-88)	0.992
Right	74.2 ± 16.5 (45-93)	71.9 ± 15.1 (28-94)	0.462
Total	72.4 ± 16.2 (32-93)	71.2 ± 15.3 (28-94)	0.663
BMI (kg/m^2)	25.7 ± 3.9	26.2 ± 4.1	0.504

*(-) symbol was solely used to indicate the left dominant hand. BMI: Body mass index; Data are expressed as mean ± standard deviation, minimum maximum, and number (percentage).

tively. The average sperm concentration was 27.2 ± 11.2 mil/cc in the group of infertile men.

Pearson correlation analysis showed that there was no significant correlation between handedness score and baseline hormone levels in both infertile men and women (all $p > 0.05$).

Discussion

It is known that reproduction is a very complex and sensitive phenomenon that both endocrine and nervous system play role in different steps including proper hypothalamic, hypophysial and ovarian function that results in live births. In this study we selected subjects with normal endocrine function and assessed the nervous system function by the utility of handedness score to predict possible nervous system malfunction in couples with IU. Previous studies tried to relate the handedness with different nervous system functions. One of the previous studies indicate that handedness is associated with auditory middle latency responses components and concluded that handedness should be considered an essential factor in the clinical or experimental use of auditory middle latency responses [18]. Another study which can be used as an evidence for handedness to be a reflection of nervous system function indicate that response of the organism to excitators at different levels and concluded that adaptation status and bioelectrical activity in right-handers and left-handers have features [19].

It was also concluded that hemispheric differences in corticospinal excitability and in transcallosal inhibition is in relation to degree of handedness [20]. Another study that assessed the relationship between the handedness and the nervous system function revealed that any changes in brain microstructure associated with left-handedness are subtle. Study speculated that the genetic contributions to left-handedness are heterogeneous in nature, with multiple different genes being involved, and the same may be true of environmental influences. Study also suggested an etiologic heterogeneity for left handedness which may manifest different brain structure and function [21].

Suggest in their study that the SON plays an important role in the communication process between the celiac-superior mesenteric ganglia (CSMG) and the ovaries as puberty approaches [22]. The number of active neurons in the CSMG varies during the rats' estrous cycle. Such changes could be related to oscillating estradiol plasma levels and to changes in the neurons' ability to be stimulated by estrogens throughout the estrous cycle. So we can suppose that there is a relationship between the degree of the brain microstructure variability and handedness degree, and this may be use to predicting the reproductive capability.

Data indicated genetic diversity results in neuronal structure diversity which may affect ovulation and spermatogenesis [5]. In our study, a statistically significant difference was observed between unexplained infertile women and control group in terms of handedness score. However, the score did not correlate with the hormone levels of the groups. At the same time, there was no statistically significant difference in hypophyseal hormone levels between the two groups. Given that the factors determining hand dominance are genetic, there is a possibility of a genetic predisposition to affect infertility in the unexplained infertile women. Further studies are needed to evaluate how a genetic background leads to this association and infertility.

To the best of our knowledge this is the first study that relate nervous system malfunction determined by the utility of handedness score in unexplained infertile cases. Drawbacks in this study are lack of gold standard tool to detect nervous system malfunction and small number of study population and we suggest further studies before reaching a final conclusion.

In conclusion, our results suggest that lower handedness score is associated with unexplained female infertility; perhaps the stress of having to operate with the non-primary hand may have resulted in compromised fertility. Additionally handedness and fertility may share a common genetic background and handedness may indirectly show the neuronal cascade function associated with the fertility problems. We think that after screening for all the fertility diagnostic tests, handedness score may be used to confirm real unexplained infertile cases. This study contributes to the debate on neuronal func-

tion in fertility by assessing handedness score, an indirect sign of neuronal function, in UI. However, future large scale studies should examine direct associations between handedness score and UI.

Conflict of Interest

None declared.

Source of Work

None declared.

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