RESEARCH ARTICLE

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Gerstmann Syndrome Case-Control Study: Correlation between Brain Lesions & Functional Disability

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ABSTRACT

Deep functional and structural neuroimaging of a series of Gerstmann's syndrome patients required high accuracy, and our results avoided false overlaps of heterogeneous brain lesions by handling each case of our study subjects separately as an individual case regarding functional and neuroimaging tests. Six patients with Gerstmann tetrad (one with dominant acalculia, one with dominant left and right disorientation, two with writing disabilities and two with finger agnosia) and 6 control subjects with close ages were recruited in the current study. In the main phase, we assessed brain activation in response to experimental and interventional settings using neuroimaging techniques (FMRI-Functional Magnetic Resonance Imaging- where twelve pictures were taken on a Dell inspiration 3T all-body scanner with sequences of echo pictures, 80° angled, TE 35 ms) of the subject's brain to declare lesions existence and locations that might result in one of the four cognitive impairment domains of Gerstman's syndrome tetrad. We assessed statistically significant differences of patient images vs. control images as well as the images of patients presenting specific symptomatic cognitive dysfunction domain vs. the images of patients presenting the three other domains. Neuroimages were analyzed using multiple databases such as T1 weighted and free sequence types. Gerstmann's syndrome is mainly connected to injury in the dominant parietal lobe, so images comparisons and analysis were only restricted to the left parietal lobe region. P values <0.05were only considered as statistically significant difference in comparisons of functional tests time and accuracy of patients vs. in addition to comparisons of brain images parameters of patient group vs. control group and specific symptomatic domain patients vs. other symptomatic domains patients. Regarding functional testing, Patients group took significantly higher time compared to control group. Regarding brain images parameters, patients in each domain showed significantly different lesions compared to other domains. Moreover, control subjects showed no lesions in the left parietal lobe compared to significant lesions in the patient groups. These results oppose the theory of Gerstmann that a common brain structural injury may result in the combination of all of the four symptomatic dysfunction domains. This may be due to the fact that Gerstmann examined incomplete cases which represent a considerable criticism to his scientific basis. Moreover, he excluded patients with speech difficulties and apraxia.

Keywords: Gerstmann Syndrome, Brain Lesions, Functional Disability, Neuroimaging.

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INTRODUCTION

Joseph Gerstmann worked in Vienna until 1938, when he travelled to New York until Nazi Germany invaded Austria (LeBron, 2005). The 53-year-old woman who experienced a cerebrovascular accident on the left-hand side was described by Gerstmann in 1924. She couldn't point her fingers or the fingers of the health care examining person, count, name, or move the examiner's fingers. When required to point to a body part using her hand, she referred to the right body part, but she could not replicate the test on the other body part. However she still kept a considerable part of her linguistic abilities. She was still able to read, speaks, and understands normally with partial difficulties in reading long sentences. She was still keeping her body parts and fingers left and right orientations with the ability to point to a specific body part with her hand[1]. In 1939, the annual Meeting (LeBron, 2005) of the Americas Psychiatry Association was held, when Gerstmann first presented his theory about the tetrad syndrome[2]. He demonstrated that the lower part of the parietal lobe is mainly affected by Gerstmann syndrome[2]. This newly discovered but intriguing syndrome became highly questionable in the 1953 Critchley research[3].

Critchley revised the history of previous Gerstmann reports and suggested that in the community of the medicine of neurological disorders, Gerstmann's syndrome was common because it proposed an understandable solution of some complicated mental disorders[4].

In his analysis of clinical features of Gerstmann syndrome, Critchley critically demonstrated that the diagnostic neurological tests were not specific enough to correlate symptoms of the tetrad to a particular brain lesion. As a medical specialist, Critchley supported the hypothesis that failure in any significant job requiring high of cognition level could be attributable to much distinct patient functional impairment. Moreover, upon critical analysis of the majority of the previously described observations, Critchley critiqued several tests Gerstmann and others presented. Because every test can examine many of the patient cognitive functions, numerous cognitive impairment mechanisms such as 'finger agnosis' or 'agraphia' may be commonly diagnosed with same test.

LITERATURE REVIEW

In 2014, an elderly patient with temp-parietal operculum and post-insular ischemic lesion and normal corner and super-marginal gyri, was also presented with dysgraphia, dyscalculia, and left disorientation (without finger agnosia).

Several years later, many publications proposed that GS may be attributed to frontal lobe lesions. In 2013, two cases published by Heymi Lee et al. Where Brain MRI detected lesions at the lower-front gyrus pars opercula is and triangularis adjacent to glioma compression and the mid-and lower-front gyrus due to hemorrhagic stroke transformed to ischemic stroke. The four symptoms of the Gerstmann tetrad were typically presented by the specific neurological testis in both cases.

Eun-Ju Lee et al (2016) reported two Brain MRI scans with the angular and supramarginal gyri ischemic lesions structurally similar to that of typical Gerstmann tetrad patients. The authors attributed such similarity to the potential for associated fibers disconnection supporting the proposal of important strong relationship between those fibers, parietal lobe and the cortical or subcortical regions on the left frontal lobe of pure Gerstmann syndrome patients.

Based on the above mentioned findings, since the insular cortex and frontal lesions were commonly detected in Gerstmann syndrome tetrad patients, the patients neurological examination changes may be definitely attributed to disconnection mechanisms secondary to lesions of fibers associating the parietal and the frontal lobes.

Putting the previously mentioned findings together with a critical discussion of the principle syndrome symptoms, Critchley proposed that Grimman's combination of the four symptoms domains was due to Grundsting defect, a "fundamental unit defect. According to Gerstmann, a certain cognitive impairment pathway is the common functional underlying mechanism of a group of variable cognitive impairment processes such as dysgraphia and dyscalculia. Moreover, many scientists who thought to link specific mental functions to certain brain regions in a trial to interpret the neuroscience fundamentals well proven based on psychological disturbances observed in patients with brain lesions. Along with these lines, it was an intellectually stimulating challenge to limit four different mental functions abnormalities to one common underlying cognitive component[5]. Cricthley reviewed all Gerstmann proposals. Gerstmann himself supported the assumption that Grundstring was a very specific impairment in the body structure, affecting various body parts such as fingers. Others considered that dygraphia, rather than finger agnosia, were the affected body element. Critchelli (1966) opposed this latter hypothesis claiming that the vertical body direction, for example, did not appear to be affected by Gerstmann's patients. Many of the above mentioned concepts have been raised based on that both the left and right body directions orientation and calculation may have underlying developmental or cultural relations with the speech ability. Till this moment, none of the supporters of the Gerstmann theory conducted a study proving the association between finger agnosia and other cognitive impairments such as acalculia in patients with brain lesions although[6].

According to Benton (1959), any of the symptoms of Gerstmann syndrome can be related to non-specific underlying cognitive impairment mechanisms. Moreover, symptoms other than those described by Gerstmann, such as speech disabilities, were found to be commonly presented by pure Gerstmann cases while not tested by Gerstmann in all cases he described[7].

The main goal of this study is to perform, deep structural and functioning examination in a number of Gerstmann's syndrome cases. Additional, to avoid probable overlap between brain lesions, we conducted our experiment using high resolution and sensitivity technique and analyzed our findings individually for each case compared to the other case and compared to the control group. In a main phase, we induced brain activation using specific neurological tests, together with brain imaging that proven to identify vulnerable cortical areas affected during the cognitive tests designed for each domain of Gerstmann syndrome tetrad dominant in each patient recruited in the current study. Moreover, brain images were critically investigated to find out common lesions, regarding site and size, using specific parameter statistical comparisons between lesions of different domains. In a subsequent phase, based on diffusion tensor imaging data, white-matter affection by activated cortical activation was assessed, where the questionable presence of a common white matter lesion in all four domains was verified.

HISTORY AND PHYSICAL

Previous studies showed that acalculia is still linked with semantic aphasia that is significantly involved in the angular gyrosis and that the Gerstmann syndrome should affect semantic aphasia.

The symptoms of Gerstmann's syndrome literally include; finger agnosia, acalculia in where patients are able to understand the numbers but cannot complete a simple addition equation, left- right disorientation and graphic, a study suggested that acalculia is mainly associated with semantic aphasia[6], which is significantly involved in the angular gyrus, where the study suggested that the syndrome should include semantic aphasia , not graphic, the later may be presented in case of superior parietal gyrus affection[8]. Thus, symptoms of this syndrome may be complete or partial[9,6] and may related to other cerebral symptoms and may occur in elderly, adult and children[10,6,11].

This syndrome may not be permanent and caused as a transient symptom in partial epilepsy, where 3 out of 4 symptoms may be presented[12].

The symptoms and signs of this disease may appear in children during late perinatal asphyxia years where transient seizure may be suffered[13].

Other signs and symptoms which may be associated with this syndrome differ according to the underlying cause such as; optic ataxia[14], cognitive impairment[15], numbness or weakness[16]. Gesture dysfunction defects and toe agnosia which may be seen as an association with finger agnosia so it may be known as digit agnosia[17].

Developmental Gerstmann's syndrome occurs in children with the tetrad of the Gerstamnn syndrome, with or without dyspraxia as an additional symptom is mainly diagnosed as Developmental Gerstmann's syndrome[11,18].

METHODOLOGY

Six volunteers diagnosed with Gerstmann syndrome (2 women, 4 men, average age 21) agreed to contribute to the study, as accepted by the Ethics Agency of Sex German. An informed consent was signed by each patient or their caregiver. Patients were diagnosed with typical tetrad symptoms and classified according to the most predominant functional disability domain as follows: (one with dominant acalculia, one with dominant left and right disorientation, two with writing disabilities and two with finger agnosia). The small sample size is mainly attributed to the limited resource available which complicates a detailed examination of larger number of pure Gerstmann syndrome. The FMRI imaging technique was mainly used, where twelve images were made on the overall 3T body scanner using a Dell-inspired echo image sequence (angle 80o, TE 35 ms). The lower parietal lobe scans, the prefrontal cortex scans and the white matter scans were assimilated to the axial sections every4sec. The whole number of the study scans taken for the six patients and control subjects can be divided as follows: 95 scans for left / right orientation tests and finger agnosia missions, 100 scan for writing tasks, and 103 scans for calculation missions. Brain images were assimilated according to the following features: TR 2.3sec, Vocal size 1.0 mm3, angle 9°, TE4.18 ms, FOV [F256mm field of view], and reverse duration 800ms In diffusion-weighted images, b factor700sec/mm2 (TE 81ms and TR 14sec) with a spin-ecological echo-planar procedure and 41 diffusion gradient orientation coding was used. 60 cross slices were needed to cover the whole brain (FOV 240mm and voxel size 1.9 1.9 2.0 mm3).

All four tests procedures were designed specifically according to the previous literature where each test has a similar sensory input and motor output. A comprehensive medical and medication history in addition to a vigorous physical examination should therefore be performed to diagnose Gerstmann syndrome and to classify the patient according to the underlying of each dominant symptomatic domain.

The neurological test conducted to differentially diagnose Gerstmann's syndrome typically consists of four basic constituents:

- Finger Agnosia: patient's eyes must be covered , and the examiner ask the patient to stretch their fingers, then the examiner should touch the patient's fingers lightly and the patient should react by finding out the touched finger as soon as it has been touched.
- Right-left disorientation: A written sentence, like "place the right hand to the left ear," should be presented to the patient and he is asked to be read it out, the physician should read the sentence on behalf of the patient if the later cannot read it correctly.
- Dysgraphia: physician should show the patient a clock, and the patient should write the its name without saying it firstly, then physician should show

the patient the word “SEVEN”, and after reading it, and presenting it orally, after that the patient should be asked to write it, then the patient should repeat the sentence “He shouted the warning” several times while explaining and writing it.

- Dyscalculia: a patient should be shown a simple equation written on a card “85-27” to write and calculate it, then the patients asked to solve a simple multiplication equation without writing or seeing it.

Brain activation impact of each test on the brain of each of the study patients and control subjects was investigated by accurately examining the taken brain scan.

The following statistical comparisons were performed:

1- Time taken by patients to finish the test compared to time taken by control subjects to finish the test.

2- Accuracy of task performance shown by patients compared to that shown by control subjects.

3-Brain images parameters of patients compared to that of control subjects.

4- Brain images parameters of each patient with dominant cognitive impairment domain compared to the rest of patents with other dominant domains.

P values < 0.05 were only considered statistically significant.

RESULTS

Time taken to finish each of the study cognitive tests was statistically higher in the patients group compared to the control group (Table 1). Moreover, task completion accuracy was statistically higher in the control group compared to the patient group. All patients had the typical four symptoms of Gerstmann syndrome. However, One patient had greater predominant acalculia where he taken statistically higher time to finish calculation test with statistically lower accuracy than the other 5 patients. The patient still take higher time to complete the test with lower accuracy than control subjects. The same was for one patient with predominant left and right disorientation, two patients with predominant writing disabilities and two patients with predominant finger agnosia.

Regarding brain images parameters, there were statistically significant differences in images parameters in patient group compared to control group. Moreover, when brain images parameters of each patient with dominant symptoms domain were compared to that of patients with other predominant domains, statistically significant differences were also detected.

DISCUSSION

In 1924, Joseph Gerstmann reported of a 53-year-old patient case presented with finger agnosia, agraphia, right-left disorientation and dyscalculia[2].

Later, in 1927, the same author described two similar cases presented with anomia for colors, apraxia, and difficulty to read numbers but not words[3]. However, when Gerstmann’s work was published in 1940, the syndrome became known among the global academic scientists. In that same year, Gerstmann syndrome tetrad was named after him comprising: agraphia, acalculia, finger agnosia and right-left disorientation[1].

Decades later, a strong association between lesions in the dominant hemisphere and Gerstmann was established, specifically angular gyrus lesions in the parietal lobe[5,6,7,16]. Such a gyrus lesion is mainly associated with agraphia and acalculia disabilities[19].

A case of a patient with non-permanent symptoms related to Gerstmann tetrad upon posterior perisylvian region stimulation, more specifically in the transition between the supramarginal gyri and the angular. He[20] reported finger recognition, calculation and writing abnormalities by the left angular gyrus brain mapping technique of 6 patients undergoing tumor resection[21].

Even in case is spared, lesions immediately angular gyrus subcortical lesions to this area and mesial occipital cortex lesions may also lead to writing and calculation disabilities. In addition[22], cases of Gerstamann syndrome cases with splenium of the corpus callosum lesions, may support disconnection hypothesis of fibers associating different cortical and subcortical[23].

In 2009, a study evaluated the applicability of the disconnection syndrome therapy to Gerstmann syndrome where the authors reviewed other certain studies that used neurofunctional imaging tractography technique. The authors suggest that Gerstmann syndrome tetrad should not be associated exclusively to a specific neuronal area. This evidence[24] supported Critchley criticism to Gerstmann theory where he questioned the neurological localizing value of Gerstmann syndrome[25].

Table 1. Statistical results.

Column1	Control (n=6)	Patients (n=6)
Calculation test accuracy (%)	98	75
Average calculation test time(Average in seconds)	102	172
Left and right orientation test accuracy (%)	99	79
Left and right orientation test time(Average in seconds)	47	100.8
Finger test accuracy (%)	98	88
Finger test time(Average in seconds)	84.1	136.6
Writing test accuracy (%)	99	72
Writing test time(Average in seconds)	165.8	200.1

While discussing the above mentioned studies results, it is important to put insular cortex area and its interaction to other cortical areas into consideration. Insular cortex area has common connections to anterior inferior parietal cortex, parietal operculum, retro insular parietal region and somatosensory cortex. Insular[26] cortex deep lesions, may result in short association fibers disconnection with subsequent front parietal circuitry disruption[27,28].

A case with ischemic lesion temporal-parietal operculum and left posterior insula lesions and normal angular and supramarginal gyri suffering dysgraphia, dyscalculia, and right-left confusion (without finger agnosia) was reported in 2014[28].

Gerstmann reported that single cognitive function impairment is particularly associated with impairment in four distinct functional domains: left–right orientation, writing, calculation, and finger gnosis. Our hypothesis is that we cannot find a common cortical lesion across the four domains, and there is no evidence for a functional commonality between them, was motivated by three considerations. First, no study reported that one cognitive model may define a single cognitive function disability that would selectively be demonstrated by the Gerstmann tetrad of symptoms. Second, electrical stimulation during open brain surgery never elicited the full tetrad of Gerstmann symptoms from a single cortical locus. Third, the best[6,7] documented lesion in a typical case was in subcortical parietal white matter. Therefore, we[1] hypothesize that Gerstmann Tetrad is mainly structural not a functional brain disorder. Separate but closely related spatial pathways may be involved in the four symptom domains with subsequent definite Gerstmnn syndrome presentation mainly by separation pathological mechanism.

The clinical and statistical results of the current study, where cortical images parameters of patients suffering a predominant Gerstmann syndrome e.g. dysgraphia domain were compared to cortical images of patients with other predominant symptoms domains (dyscalculia, finger agnosia and left-right disorientation), a statistically significant difference at p values > 0.05 was found, support the above mentioned studies and theories criticizing the old Gerstmann hypothesis that all Gerstmann syndrome symptoms domain may be a result of a localized lesion only affecting the lower parietal lobe.

CONCLUSION

Our review of the literature in addition to the current study findings lead us to believe the hypothesis that the observed neurological exam changes in Gerstmann syndrome patients may have been attributed disconnection mechanism secondary to ischemic injury of the association fibers connecting frontal and parietal lobes, given that lesions were present in the insular cortex of the dominant hemisphere and the inferior frontal gyrus.

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