Brain-derived neurotrophic factor and coenzyme Q10 levels in blood of children with learning disorder

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Background
Learning disorder (LD) is manifested by significant difficulties in the acquisition and use of reasoning, reading, writing, or mathematical abilities, despite average intelligence and proper education. Its etiological factors were suggested to be related to neurodevelopmental alterations. Measurement of the levels of brain-derived neurotrophic factor (BDNF) and coenzyme Q10 (CoQ10) was targeted in children with LD in comparison with typically developing (TD) ones.
Materials and methods
This study included 82 Egyptian Arabic-speaking children matched for age and sex and socioeconomic status, comprising 42 with specific LD (group I) and 40 TD children (group II). All participants were subjected to clinical and full neurological examination after reporting a full medical history. Furthermore, LD group was subjected to Stanford–Binet intelligence scale, dyslexia assessment test, and phonological awareness test, which evaluates cognitive and learning aptitudes. The levels of BDNF and CoQ10 were determined in serum by enzyme-linked immunosorbent assay.
Results
All children with LD obtained a score of 1 or more as at-risk quotient by the dyslexia assessment test, which indicated a specific reading disorder. The BDNF and CoQ10 levels in the LD group were significantly less than those in the TD group. No correlations were found between the measured markers and each other or between them and the measured factors of the used tests.
Conclusion
The detected low levels of BDNF and CoQ10 in children with specific LD with impairment in reading would be suspected to be related to etiological or exaggerating factors for the deficits in such children.

Keywords:
brain-derived neurotrophic factor, coenzyme Q10, learning disorder

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Introduction

Learning disorder (LD) is a neurodevelopmental disorder that leads to impairment in reading, writing, or mathematical skills in school-aged children in spite of absence of intellectual disability and despite having proper educational opportunity. The most common form of this disorder is LD with impairment in reading or developmental dyslexia [1]. The exact etiological factors for this complicated disorder have not been yet underpinned. An interaction among genetic, epigenetic and environmental factors has been suggested. LD is presumed to be due to central nervous system dysfunction and biochemical alterations that originate during developmental period but do not influence the general intelligence [2].

A neurotrophin brain-derived neurotrophic factor (BDNF) is widely distributed in brain regions such as the hippocampus, cortex, cerebellum, and basal forebrain [3]. During prenatal development, BDNF is minimal. Postnatally, the level of BDNF rises to much higher levels [4]. Currently, it is believed to be the most broadly distributed and abundant neurotrophic factor in the brain of adult humans [5]. BDNF plays a critical role in the brain functions through its two independent receptors: tropomyosin-related kinase B and p75. The tropomyosin-related kinase B receptor belongs to a large family of receptor tyrosine kinases, which has three isoforms that have been found till now. The full-length isoform is a typical tyrosine kinase receptor which transduces the BDNF signal [6]. Important functions in neuronal growth and plasticity, cell survival, and differentiation especially in the hippocampus and prefrontal cortex were played by

BDNF. These areas are crucial for learning and memory [7,8].

Memory development is very substantial for the process of learning. Impaired BDNF functioning was found to cause impaired long-term and short-term types of memory [9]. Memory impairment was reported in children with developmental dyslexia [10]. Therefore, the BDNF levels could differ in individuals with LD especially developmental dyslexia. The relation between BDNF levels and the cognitive performance in animals and humans was investigated. Nevertheless, these studies are still in their infancy and have not targeted children with specific LD, especially developmental dyslexia [11,12].

Coenzyme Q10 (CoQ10) is a component of the electron transportation chain and participates in aerobic cellular respiration. It generates energy in the form of ATP. It contains a chain with 10 isoprenoid units and is therefore referred to as CoQ10 [13]. It protects mitochondrial membrane protein and cellular membrane phospholipids. Under pathological and physiological conditions, an important role in the redox cellular status modulation was played by the antioxidant property of CoQ10 [14]. It has been reported that CoQ10 supplementation has an enhancement action on learning and memory in human and animal studies [15,16]. However, changes in its level have not been previously investigated in children with LD. Abdelraouf *et al.* [17] suggested that children with LD manifest memory and linguistic deficits which could be related to oxidative stress. Thus, both BDNF and CoQ10 are suspected to differ in children with LD.

This study aimed at comparing the levels of BDNF and CoQ10 in the blood of children with LD and typically developing (TD) children. Correlation between the determined blood levels of BDNF and CoQ10 was investigated.

Materials and methods

Inclusion and exclusion criteria

The inclusion criteria for LD group of children were meeting the diagnosis of specific LD according to the criteria of DSM-5 [1], complaining of poor scholastic achievement, and obtaining an intelligence quotient (IQ) of 85 or more by the Stanford–Binet intelligence scale 4th edition [18,19]. The participants were native Arabic speakers who were enrolled in the national education system. Children who had associated neurological and/or psychiatric disorders were excluded from the study. Moreover, children who had a history of developmental delay were excluded. For group II, the inclusion criteria were the enrollment in the national education system with good school performance and being Arabic native speakers.

Study design

A total number of 82 Egyptian Arabic-speaking children were included in this cross-sectional, comparative, case–control study, and classified into two groups as follows:

(1) Group I included 42 (28 boys and 14 girls) of them who manifested LD. Their age ranged from 6.5 to 12 years and the IQ ranged from 85 to 116. They visited the learning disability research clinic, phoniatric research clinic, and pediatric neurology research clinic, Medical Research Center of Excellence, Medical Research Division, National Research Center, Cairo.
(2) Group II included 40 TD children (25 boys and 15 girls, with age ranged from 6.5 to 12 years) who did not have any neurological or psychiatric disorders. They were enrolled from the relatives of participants.

The two groups had the same socioeconomic status, which was evaluated during history taking by asking about the education of the parents of participants. They all obtained high education. Furthermore, we asked about the average income for the family, and it was similar to average middle-class family.

Ethical approval

Informed consents were obtained from the parents of all participants. This study was approved by the Medical Research Ethics Committee of the National Research Center, Cairo, Egypt, with approval number 18182.

Methods

Clinical and learning disorder tests

Participants in group I were subjected to clinical and full neurological examination after reporting a full medical history, clinical examination, and Mini International Neuropsychiatric Interview for Children kid [20,21] which was used to verify the absence of any associated psychiatric disorder. The details of subitems of the Stanford–Binet intelligence scale 4th edition were obtained [18,19]. Furthermore, the participants in group I were subjected to dyslexia assessment test. It is a test that evaluates reading, writing, spelling, and some relative cognitive abilities of school-aged children. The raw scores of the

subsets were used to determine the quality of the performance guided by tables for each certain age group. An at-risk quotient is finally obtained. When the at-risk quotient is one or more than one, it indicated a specific reading disorder or the presence of dyslexia. This quotient increases with the worse performance in the tested abilities [22,23]. The phonological awareness test was concerned with evaluating word awareness, syllable awareness, rhyme awareness, phoneme awareness (isolation-deletion and substitution: at the beginning, the end and the middle of word; blending and segmenting phonemes), grapheme-phoneme correspondence, and sound production ability in Arabic [24]. In addition, electroencephalogram was performed for all participants.

Sample collection and biochemical analysis

Venous blood samples from both groups were obtained in 5 ml vacutainer tubes. They were left to clot and then centrifuged at 3000 rpm for 10 min. The clear supernatant serum was then separated and frozen at −20°C for the biochemical analysis. The serum BDNF level was determined according to Hashimoto *et al.* [25] using the human BDNF enzyme-linked immunosorbent assay kit of Adipo Bioscience Co. (Santa Clarita, California, USA). CoQ10 was also determined according to Mousavinejad *et al.* [26] using enzyme-linked immunosorbent assay kit of My BioSource Co. (Rue de Bosquet, Louvain-la-Neuve, Belgium).

Statistical analysis

Results were represented as mean±SD and analyzed using the statistical package for the social sciences (SPSS) software computer package version 17 (SPSS Inc., Chicago, Illinois, USA). Difference was considered significant when P value less than 0.05 using Mann–Whitney U-test.

Results

The subitems of the Stanford–Binet intelligence scale are presented in Table 1. The most defective item was working memory, whereas the scores of other items were nearly similar. All children in group I obtained 1 or more than 1 as at-risk quotient by the dyslexia assessment test (range: 1–3.1; mean: 1.7±0.5). Therefore, they all had developmental dyslexia (specific LD with impairment in reading). The percentage of children who manifested deficits in the evaluated aptitudes was the highest in nonsense passage reading and verbal fluency abilities of the dyslexia assessment test. Most of LD cases manifested a phonological awareness deficit (Table 2). None of the participant manifested electroencephalogram changes or associated psychiatric disorder such as Attention Deficit Hyperactivity Disorder (ADHD) according to Mini International Neuropsychiatric Interview for Children kid.

Brain-derived neurotrophic factor and coenzyme Q10 levels

The present findings revealed a significant decrease of the blood BDNF in the LD group (1.1±0.24 ng/ml) when compared with the control group (2.00±0.4 ng/ml). Furthermore, there was a significant decrease in CoQ10 levels in the LD group (0.65±0.37 μmol/l) when compared with the control group (1.22 ±0.57 μmol/l), as shown in Table 3, using the Mann–Whitney U-test.

Table 1 The mean and SD of the total intelligence quotient and the subitems of the Stanford–Binet intelligence scale 4th edition in the learning disorder group (group I)

The subitem	Learning disorder group (group I)	Range
Verbal reasoning	96.1±10.4	90–107
Abstract/visual reasoning	97.6±14.3	66–118
Quantitative reasoning	97.6±10	89–110
Working memory	93±13.2	59–124
Total intelligence quotient	95.5±6.1	85–116

All data were expressed as mean±SD.

Table 2 The mean, SD, and the approximated percentage of manifested deficits in the sub-tests of the dyslexia assessment test, the at-risk quotients, and the scores of the phonological awareness test in the learning disorder group (group I)

The aptitudes	Scores (mean±SD)	The nearly percentage of cases showing deficit
Rapid naming test	86.5±40.6	88
Bead threading	5.4±1.9	19
One minute reading	10.6±11	26
Postural stability	7.4±4	17
Phonemic segmentation	5±3.8	71
Two minute spelling	6±6.7	67
Backward digit span	3.3±1.8	60
Nonsense passage reading	14.8±14.5	95
One minute writing	7.5±4.4	83
Verbal fluency	3.1±2.2	95
Semantic fluency	8.7±2.8	74
At-risk quotient	1.7±0.5	100
Phonological awareness score	74±27.3	67

All data were expressed as mean±SD.

Table 3 Comparison between brain-derived neurotrophic factor and the coenzyme Q10 in the two groups

Measured markers	Learning disorder group (group I) (mean±SD)	Control (group II) (mean±SD)	χ^2	*P* value
Brain-derived neurotrophic factor	1.1±0.24	2.00±0.4	6.1	<0.05*
Coenzyme Q10	0.65±0.37	1.22±0.57	5.3	<0.05*

All data were expressed as mean±SD. *$P<0.05$, significant differences than control group.

Table 4 Correlation results between the brain-derived neurotrophic factor and other measures in learning disorder group (group I)

Title	*R* value	*P* value
Brain-derived neurotrophic factor	0.01	0.90
Chronological age	–0.03	0.8
Verbal reasoning	–0.09	0.6
Abstract/visual reasoning	0.3	0.1
Quantitative reasoning	0.2	0.3
Working memory	–0.05	0.8
Total intelligence quotient	0.4	0.06
At-risk quotient	–0.1	0.4
Phonological awareness score	–0.1	0.5

*$P<0.05$, significant differences than control group.

Correlation analysis

Correlation analysis between the estimated serum BDNF and CoQ10 revealed no correlation between the two measures in the LD group (r=–0.01; P=0.90) or in the control group (r=0.29; P=0.06). Furthermore, no correlation was found between the measured markers and the chronological age in both groups. Correlation analysis between the measured markers in group I and the total IQ and the subitems of the Stanford–Binet test, at-risk quotient of dyslexia assessment test, and phonological awareness test scores revealed insignificant correlation ($P>0.05$; Tables 4 and 5).

Sensitivity and specificity of the measured biochemical markers

The data presented in Fig. 1 show that the BDNF at the level of 1.35 (cutoff value) has a 92% sensitivity and an 85% specificity, whereas the CoQ10 at a cutoff value of 1.43 has a 97% sensitivity and 62% specificity.

Discussion

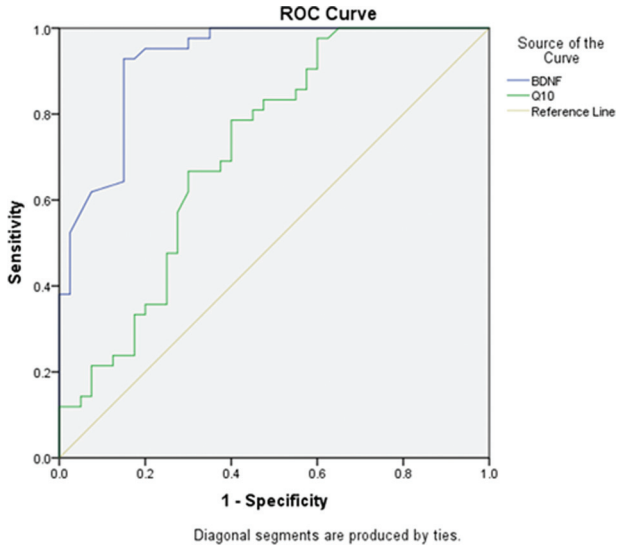
Regarding their participation in underpinning possible etiological factors of LD, the blood levels of BDNF and CoQ10 were estimated for cases in comparison with TD children. Possible relations between these estimated measures were also investigated. The memory subtest of the Stanford–Binet intelligence scale was the least

Table 5 Correlation results between the coenzyme Q10 and other measures in learning disorder group (group I)

Title	*R* value	*P* value
Coenzyme Q10	0.01	0.90
Chronological age	–0.04	0.8
Verbal reasoning	–0.3	0.09
Abstract/visual reasoning	–0.09	0.6
Quantitative reasoning	0	1
Working memory	–0.41	0.06
Total intelligence quotient	–0.2	0.3
At-risk quotient	–0.1	0.4
Phonological awareness score	0.3	0.06

*$P<0.05$, significant differences than control group.

Figure 1



The receiver operating characteristic curve for the brain-derived neurotrophic factor and the coenzyme Q10 in the learning disorder group (group I).

score obtained by the participants, which is in agreement with previous reports that targeted Arabic children with LD or dyslexia such as Abdelraouf *et al.* [17]. Furthermore, the common presence of deficits in phonological awareness and verbal fluency among LD participants is in agreement with Allam *et al.* [10], who reported common deficits detected in a sample of children with developmental dyslexia.

BDNF is a neurotrophin expressed in the brain throughout life and serves as neurotransmitters modulator. BDNF is involved in mechanisms of learning, long-term potentiation, and neuronal plasticity. BDNF is required for the development of the nervous system, proper memory formation, and cognitive function [27]. These cognitive functions include capabilities such as attention, executive functioning, assessing, and monitoring [28]. BDNF causes an increase in the number of dendrites on neurons and in synaptic neurotransmitter receptors,

which then increases connectivity and neuroplasticity in the brain. The balanced formation of additional receptors and neurons causes a more efficient learning and memory capacity and improves overall brain function. BDNF protein crosses the blood–brain barrier, and blood BDNF concentrations have a high positive correlation with cortical BDNF protein levels [4]. Therefore, blood levels of BDNF could reflect its status in the brain. The present study showed a significant decrease in BDNF content in the blood of LD group when compared with control group.

Aberrant expression of BDNF has been implicated in neurological disorders [27]. It has been proposed that a decreased midbrain BDNF activity may cause midbrain dopaminergic dysfunction [29]. Furthermore, BDNF is widely expressed in hippocampus and hypothalamus. It has been related to serotonin system functioning in areas related to memory and motivation [30]. Therefore, reduced BDNF levels could have a negative effect on the proper development of neural circuits which are essential for learning. Previous studies revealed reduced blood BDNF levels in neuropsychiatric disorders such as major depressive disorder and Parkinson's disease, which both manifest memory deficits [31,32]. However, no previous study has investigated the BDNF levels in children with LD.

This study further indicated a significant decrease in blood CoQ10 in patients with LD. Because of its involvement in ATP synthesis, CoQ10 is essential for the health of organs and tissues especially neuronal tissues. The functions of all cells in the body, especially cells with high-energy demand, were affected by CoQ10. Thus, it is essential for the health of tissues and organs especially neural tissues. It is the only lipid-soluble antioxidant synthesized endogenously, and it efficiently prevents oxidation of proteins, lipids, and DNA. CoQ10 is involved in lipid metabolism and neuronal cell migration. Neurons have constant high-energy demands. Moreover, the nervous system is exposed to and vulnerable toward oxidative stress, which highlights the CoQ10 role in the nervous system [33]. Oxidative stress leads to oxidative damage in lipids, proteins, and nucleic acids. From clinical studies, it is clear that a large number of neurological disorders may be caused by oxidative stress and its consequences [34].

CoQ10 improves the cell and mitochondrial membrane barrier properties by variable mechanisms depending on the lipid composition of these membranes. The interaction between CoQ10 and lipid layers has been reported to be influenced by the nature of the lipid head group, the acyl-chain length, and the degree of unsaturation. Thus, it was reported to be strongly related to the inner mitochondrial membrane integrity [13]. Although some of its effects may be related to a gene induction mechanism, CoQ10 was used widely in clinical applications owing to its well-known antioxidant properties and its fundamental role in mitochondrial bioenergetics [35]. Additionally, the role of CoQ10 in oxidative phosphorylation emphasizes its importance in the metabolism of neurons. Consequently, its deficiency is expected to result in malfunctioning of neurons in the central nervous system. This would have a damaging influence on brain areas responsible for memory. This was previously reported in neurological disorders that have impairment in memory functioning such as Parkinson's disease and Alzheimer's disease [36].It is worth noting that CoQ10 and BDNF have been linked to cerebellar functioning. Cerebellum has been reported to be functionally and anatomically altered in specific LD with impairment in reading (developmental dyslexia) [37]. The relation between BDNF and CoQ10 could stem from their importance for the mitochondrial functioning. They both have antioxidant function. Furthermore, supplementation of CoQ10 has been reported to cause an increase in BDNF [38]. The absence of correlation in the LD group could imply a disturbance in such relation which could be related to the oxidative stress status or mitochondrial dysfunction. These derangements were previously reported in children with LD [13–17].

The significant changes in the levels of BDNF and CoQ10 could propose possible biomarkers for specific LD with impairment in reading or developmental dyslexia. Calculating the sensitivity and specificity for the measured biomarkers indicated that the BDNF has very high sensitivity and specificity. CoQ10 obtained lower area under the curve than BDNF and less specificity but had high sensitivity. This was noticed despite the absence of correlation with the evaluated aptitudes. Therefore, CoQ10 could be an exaggerating factor that increases the oxidative stress in such population. The high sensitivity and specificity for the BDNF underscores its role as a biomarker for LD and suggests its involvement in the pathogenesis of specific LD.

Conclusion

BDNF and CoQ10 levels could be contributors to etiological or exaggerating factors of the specific LD

as manifested by their decreased levels in children with LD with impairment in reading (developmental dyslexia). This would suggest their use as biochemical markers for specific LD with impairment in reading.

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Conflicts of interest

There are no conflicts of interest.

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