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Do Low Serum UCH-L1 and TDP-43 Levels Indicate Disturbed Ubiquitin-Proteosome System in Autism Spectrum Disorder?

İhsan ÇETİN[1], İhsan TEZDİĞ[2], Mahmut Cem TARAKÇIOĞLU[3], Muhammed Tayyib KADAK[4], Ömer Faruk DEMİREL[5], Ömer Faruk ÖZER[6], Fırat ERDOĞAN[7], Burak DOĞANGÜN[4]

[1]Department of Nutrition and Dietetics, Batman University School of Health, Batman, Turkey
[2]Department of Chemistry, Batman University Institute of Science, Batman, Turkey
[3]Department of Child and Adolescent Psychiatry, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkey
[4]Department of Child and Adolescent Psychiatry, İstanbul University Cerrahpaşa School of Medicine, İstanbul, Turkey
[5]Department of Psychiatry, İstanbul University Cerrahpaşa School of Medicine, İstanbul, Turkey
[6]Department of Biochemistry, Bezmialem Vakif University School of Medicine, İstanbul, Turkey
[7]Department of Pediatrics, Medipol University School of Medicine, İstanbul, Turkey

ABSTRACT

Introduction: The mechanism of ubiquitination-related abnormalities causing neural development problems is still unclear. We examined the association between autism and serum transactive response DNA-binding protein-43 (TDP-43) and ubiquitin c-terminal hydrolase-L1 (UCH-L1) levels, both of which are members of the ubiquitin-proteosome system.

Methods: We measured serum levels of TDP-43 and UCH-L1 in 24 children with autism and 24 healthy children. Childhood Autism Rating Scale (CARS) was used to assess symptom severity at admission.

Results: The mean serum TDP-43 and UCH-L1 levels in children with autism spectrum disorder (ASD) were found to decrease compared to healthy controls ($p<0.001$, 506.21±780.97 ng/L and 1245.80±996.76 ng/L, respectively; 3.08±5.44 ng/mL and 8.64±6.67 ng/mL, respectively). A positive correlation between serum TDP-43 levels and UCH-L1 levels was found in the ASD group ($r=0.947$, $n=24$, $p<0.001$). The CARS score of children with ASD was 48.91 points (standard deviation [SD]: 5.82).

Conclusion: Low serum levels of UCH-L1 and TDP-43 may reflect disturbed ubiquitination in autism.

Keywords: Autism, UCH-L1, TDP-43, ubiquitination

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INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in communication, social interaction, and increased repetitive behavior. ASD has a complex genetic contribution interacting between multiple genes and environmental factors (1). However, an exclusive explanation for the etiopathogenesis of autism has not yet been provided.

The ubiquitin-proteasome system (UPS) is a major non-lysosomal proteolytic process that regulates the levels of cellular proteins including those involved in neuronal growth and function. Findings have suggested that ubiquitination and related proteins play major roles in synaptic plasticity (2,3). Furthermore, the UPS system is involved in neurodegenerative disorders, such as Alzheimer's and Huntington's disease (3). In addition, deficit or excess ubiquitin-protein ligase E3A (UBE3A) leads to autistic symptoms in the Angelman syndrome. UBE3A is regulated by phosphorylation and an autism-linked mutation causes regulation impairment of phosphorylation and synapse formation (4,5). Abnormal UBE3A activity is believed to contribute to neuropathological features in autism (5). As phosphorylation of UBE3A enables synapse development, a close relationship between phosphorylation of ubiquitination and dendritic spine density has been reported (5,6,7,8,9,10). Moreover, in UBA6 brain-specific knockout mouse, it was revealed that autistic symptoms were observed in the absence of UBA6 (1). Therefore, abnormalities in ubiquitination system might be related with autistic pathology.

There are some molecules in the UPS, however brain and blood levels or pathophysiological role of these molecules have not been investigated in autism. Ubiquitin C-terminal hydrolase-L1 (UCH-L1), a 223-amino acid protein (25 kDa) is highly and specifically expressed in neurons, and has been used as a histological marker (11,12). It is involved in the process of ubiquitination of proteins destined for degradation via the proteosomal pathway to remove oxidized or misfolded proteins (13). UCH-L1 has been reported to be associated with Parkinsons disease

Correspondence Address: Mahmut Cem Tarakçıoğlu, Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi, Çocuk ve Ergen Psikiyatrisi Anabilim Dalı, İstanbul, Türkiye E-mail: mtarakcioglu@hotmail.com

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(PD) and traumatic brain injury (TBI) (14). Interestingly, it was found that gene deletion of UCH-L1 leads to progressive loss of the dopaminergic neurons in substantia nigra and striatum (15,16).

Another molecule related to ubiquitination, the transactive response DNA-binding protein (TDP-43), has been considered in neurodegenerative disorders, such as Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Lobar Degeneration (FTD) (17). TDP-43 inclusions were observed in Alzheimer's disease, Guam parkinsonism-dementia complex, Huntington's disease, and Hippocampal sclerosis (18,19,20,21). Physiologically, TDP-43 shuttles between the nucleus, where it regulates transcription and splicing, and the cytoplasm, where it has a role on RNA transport and mRNA stability and is a component of stress granules (3,17). Most ALS patients show TDP-43 pathology in postmortem tissue. TDP-43 is abnormally ubiquitinated, phosphorylated, cleaved, translocated to the cytoplasm and found as aggregates in the (upper and lower) motor neurons (17,21).

Considering these aspects, we hypothesized that widespread TDP-43 and UCH-L1 proteinopathy may underlie multifocal neuronal dysfunction that contributes to complex nonmotor phenotypes in autism, including cognitive impairment with prominent frontal executive dysfunction and extrapyramidal signs. In this regard, we aimed to investigate the serum levels of TDP-43 and UCH-L1 in children with autism.

METHODS

Participant Samples

In total, 24 children with ASD and 24 controls were enrolled in the study. The children in the first group were diagnosed as having autism according to the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., criteria. In pediatric clinics of Medipol University Hospital, age- and sex-matched children were recruited as the healthy control group. Eligible children in the control group were evaluated by child psychiatrists. The ethics committee of İstanbul University Cerrahpaşa School of Medicine approved the present study. Consent forms were obtained from parents of the participants.

Childhood Autism Rating Scale (CARS) was used to assess severity of autistic symptoms. CARS consists of 15 categories, each is rated on a four-point scale. An individual is considered as mild-to-moderate when scores are between 30 and 36 and severely autistic when score are between 37 and 60. The Turkish language version of CARS was used in previous studies (22).

Procedure

Blood samples were collected after a ≥12 h fast. Blood specimens were allowed to clot for 30 min. They were routinely centrifuged at 4000 rpm for 10 min, and aliquots of serum samples were stored at −70°C for measurement of TDP-43 and UCH-L1 concentration.

Measurement of TDP-43 and UCH-L1

Serum concentrations of TDP-43 and UCH-L1 were determined with the enzyme linked immunosorbent assay method (YEHUA Biological Technology, China, Catalog Number YHB3139Hu and YHB3139Hu, respectively) according to the manufacturer's instructions. Briefly, samples were added to wells that are precoated with monoclonal antibody and incubated further; subsequently, biotin-labeled antibodies were added, and combined with streptavidin-horse radish peroxidase to form an immune complex; incubation and washing steps were performed. Chromogen solutions were then added, and the addition of stop solution resulted in yellow coloration. The absorbance was measured at 450 nm. Assay ranges of these kits were 20 ng/L→6000 ng/L for TDP-43 and 1 ng/mL→38 ng/mL for UCH-L1.

Table 1. Characteristics of the autism and control groups

Variables	Autism (n=24)	Control (n=24)	p
Demographics			
Age, mean (SD)	3.41 (0.92)	3.37 (0.76)	p>.05
Males, n (%)	18 (%75)	16 (%66.7)	p>.05
CARS, mean (SD)	48.91 (5.82)	-	
IQ score, mean (SD)	33.37 (10.89)	-	
Laboratory findings			
Serum TDP-43 (ng/L)	506.21±780.97	1245.80±996.76	p<0.001
Serum UCH-L1 (ng/mL)	3.08±5.44	8.64±6.67	p<0.001

CARS: childhood autism rating scale; IQ: intelligent quotient; TDP-43: transactive response DNA-binding protein-43; UCH-l1: ubiquitin c-terminal hydrolase-L1; ng: nanogram; L: leter; mL: milileter; SD: standart deviation; n: number

Statistical Analysis

Univariate data were compared using the chi-square-test for categorical variables and Mann-Whitney test. Spearman correlation analyses were applied between UCH-L1 and TDP-43. A p value of <0.05 was considered significant. Statistical package for Social Sciences for Windows, v.17.0 (SPSS Inc.; Chicago, USA), was used for statistical analyses

RESULTS

Table 1 shows sociodemographic data of the groups; 75% of the participants were boys in the ASD group, and the mean age was 3.41 years (standard deviation [SD]: 0.92), while 66.7 % were boys in the controls, and the mean age was 3.37 years (SD: 0.76). The ASD group had no familial autism history. The mean serum TDP-43 levels were found to be significantly lower in the children with ASD compared with controls (p<0.001; 506.21±780.97 ng/L and 1245.80±996.76 ng/L, respectively). The mean serum UCH-L1 levels significantly decreased in the ASD group compared with controls (p<0.001; 3.08±5.44 ng/mL and 8.64±6.67 ng/mL, respectively). Significant positive correlation was found between serum TDP-43 and UCH-L1 levels (r=0.947, n=24, p<0.001). The mean CARS score of the ASD group was 48.91 points (SD: 5.82).

DISCUSSION

In recent genetic studies, it has been suggested that there is an increased risk of autism with proteins related to synapse formation (23). UPS was considered important for regulating synaptic protein functions, particularly in the synapse. As previously shown, molecules that are involved in ubiquitination play a significant role in brain development processes, such as synaptogenesis, as the balance between ubiquitination and deubiquitination is critical for synapse function (5,24). For example, regulation of ubiquitination via UBE3A with phoshorylation was impaired, and it led to increased synapsis and dendritic spine density in an autism proband with a mutant of T485 (4,5). To our knowledge, this is the first research investigating UCH-L1 and TDP-43 serum levels in ASD, in which both molecules are involved in protein formation. These preliminary study findings revealed that serum UCH-L1 and TDP-43 levels of ASD patients were significantly lower than those in the healthy control group. Similarly, UBE3A, which is another important molecule in the ubiquitin system, was found to be associated with autistic symptoms in the Angelman syndrome

(25,26). Therefore, impairment in UPS might show the underlying mechanism of synapse pathology in autism.

UCH-L1 and the UPS molecule are thought to be essential for synaptic function and cognition (27,28,29). Altered ubiquitination resulting from abnormal UCH-L1 expression may contribute to learning and memory impairment (30). According to these aspects, mouse models in ASD, such as UBA6 brain-specific knockout mouse, suggest a relation of ubiquitination and autism. Lee et al. (1) revealed that the UBA6 deficit in the neuronal tissue leads to autistic symptoms. Beyond these, Angelman syndrome is caused by lack of or excess of UBE3A, which leads to autistic features (31). In addition to UBE3A, it was revealed that there was association between synaptic pathology in autism and other ubiquitin genes, including SHANKS, RFWD2, FBXO40, and PARK2 (32,33). Furthermore, increased UBE3A in the synapse leads to suppression of glutamatergic signaling. This might show a mediator effect of UPS (e.g., UBE3A, UCH-L1, and UBA6, genes including SHANKS, RFWD2, FBXO40, and PARK2) associated with neuronal activity (32). Therefore, decreased serum level of UCH-L1 may reflect underlying problems in UPS. However, our findings have to be confirmed by cell-based studies.

TDP-43, an RNA binding protein, dynamically plays a role in synaptic activity (34). It was demonstrated that alteration in TDP-43 regulation in the early phases of development might lead to neurodegeneration (35). Moreover, TDP-43 protein aggregated in FTD and ALS was shown in ubiquitinated neuronal cytoplasmic inclusions either in central or peripheral neurons (17). However, TDP- 43 has been recently demonstrated to have multiple roles in the regulation of the mRNA fate in neuronal cells, such as transcript stabilization and activity-dependent transport to dendrites (36,37). TDP-43 homeostasis might be maintained by UPS and autophagy (38). Such ubiquitination, abnormal hyperphosphorylation, and N-terminal cleavage 43 modifications were revealed in FTLD and ALS patients (39). These findings were interpreted as playing a vital role in the early development. Similarly, low serum level of TDP-43 in our study may show disturbed UPS leading to altered development of synapse in autism.

While TDP-43 and UCH-L1 are typically regarded as intracellular proteins, they have however been discovered to be normally present in extracellular biological fluids, including human cerebrospinal fluid (CSF) and blood plasma (40). It was thought that increased CSF level of TDP-43 might highlight a critical effect of TDP-43 level in neuronal functions (41). Furthermore, UCH-L1, which is abundant in the body of neurons in the central nervous system, was a biomarker of neuronal injury that shows elevated CSF and serum UCH-L1 levels in an ischemic stroke model (42). However, this was not found in intracranial hemorrhage (43). It has been also revealed that increased serum levels of UCH-L1 reflect neuropathology, such as subcortical white matter lesion and increased level of UCH-L1 level in the CSF (44,45). Thus, UCH-L1 was suggested as an indicator of TBI. As shown in both elevations of UCH-L1 levels in response to neuronal injury, low serum levels might be a reflection of disturbed neuroplasticity in autism. In addition, another important finding of our study was the positive correlation of these two molecules. As both molecules are involved in UPS, this association may the support role of UPS in autism. Thus, our study revealed that molecules involved in ubiquitination may influence the autistic behaviors. Probably, an unexplained mechanism underlies the pathogenesis of autism, for example, UCH-L1 may play a role in the underlying mechanism in autism via ubiquitination (14). Thus, we thought that low serum levels of UCH-L1 and TDP-43 may indicate subtle dysregulation of ubiquitination in the cellular aspect of autism (1). However, further studies are required to support these results.

There are several limitations in the present study. Therefore, our study should be considered as a preliminary study. Firstly, the range of our study samples was small. Secondly, we collected only serum samples, while CSF samples were absent. Thirdly, reliability and validation of CARS have not yet been confirmed for the Turkish population, while study has been conducted.

Low serum levels of UCH-L1 and TDP-43 may imply disturbed ubiquitination in ASD. Since protein ubiquitination is a universal reaction occurring in almost every physiological process within the cell, the reason for ubiquitination-related molecular abnormalities in neural development has not been explained. There may be some signatures in functionally important proteins, which are processed during neural development. Further studies are required to identify the underlying pathogenesis of ASDs.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University Cerrahpaşa School of Medicine (01.04.2014/A-43).

Informed Consent: Written informed consent was obtained from the parents of the patients who participated in this study.

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