



Research Paper: Analysis of Soluble Mesenchymal-Epithelial Transition Factor and Hepatocyte Growth Factor Serum Levels in Children With Autism Spectrum Disorder



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Running Title Serum Met and HGF in Different Stages of Autism
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ABSTRACT

Background: Hepatocyte Growth Factor (HGF) and its receptor, Mesothelial-Epithelial Transition (cMet) factor signaling, play an essential role in controlling synaptogenesis.

Objectives: Because of the vital role of HGF and Met signaling in synaptogenesis and spatial learning function of the brain's hippocampal region, we aimed to study the HGF and soluble cMet (s-cMet) serum levels in children with different stages of Autism Spectrum Disorders (ASD).

Materials & Methods: A total of 189 ASD patients (mild; n=69, moderate; n=63 and severe; n=57) and 82 control were enrolled in this project. Blood samples were collected from ASD patients referred to Pediatric Neurology Clinic, 17 Shahrivar Hospital, Rasht City, Iran, and serum concentrations of s-cMet and HGF were measured by ELISA. The control children with no clinical characteristics of ASD attended routine blood tests.

Results: HGF Mean±SD serum concentration in ASD patients was 239±52.02 pg/mL compared to controls which was 360.04±71.15 pg/mL (P=0.004). Also, the Mean±SD serum concentrations of HGF in mild, moderate, and severe ASD patients were 297.54±69.82, 232.81±56.41, and 189±33.25 ng/mL, respectively, compared to control, which was 360.18±57.40. Besides, the s-cMet Mean±SD serum concentrations in ASD and controls were 143.54±32.50 and 200.25±31.16 pg/mL, respectively (P=0.005). The Mean±SD serum concentrations of s-cMet in the mild, moderate, and severe ASD patients were 172.81±37.69, 129.81±45.55, and 85.18±22.95 ng/mL, respectively, as compared to the control, which was 214.54±34.17 ng/mL.

Conclusion: Serum HGF and s-cMet concentration decreased in ASD patients corresponding to disease severity. Also, detecting serum HGF and s-cMet may help classify ASD.

Keywords: Hepatocyte growth factor, Serum, Autism Spectrum Disorder

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Highlights

- Hepatocyte Growth Factor (HGF) and soluble cMesenchymal-epithelial growth factor (s-cMet) are a constant composition of human serum.
- Serum HGF and s-cMet concentrations are high in Autism Spectrum Disorder (ASD) patients.
- Serum HGF and s-cMet concentrations are negatively associated with the severity of ASD.
- Detection of serum HGF and s-cMet may help classify ASD.

Introduction

Autism Spectrum Disorder (ASD) is characterized by difficulty in social communication and having restricted, repetitive behavior patterns, interests, or activities. The worldwide prevalence of autism is just under 1%, but estimates are higher in high-income countries [1]. The incidence of ASD seems to be increasing worldwide [2]. The complex pathophysiology of ASD encompasses interactions between genetic and environmental factors. Hundreds of genes, converging at the functional level on selective biological domains, such as epigenetic regulation and synaptic function, have been identified as either causative or risk factors of autism [3].

Growth factors like hepatocyte growth factor (HGF) and its receptor, mesothelial-epithelial transition factor (cMet) signaling, play an essential role in controlling neuron maturation and synaptogenesis [4]. The HGF gene map to 7q21.11 in the same chromosomal region of its receptor Met. The *MET* gene is located on 7q31 and encodes a 1390 aa protein, with an apparent molecular weight of 190 kDa [5]. *MET* activation during neocortical neuron growth and synaptogenesis, with distinct biological outcomes mediated by distinct Met-linked intracellular signaling pathways in the same neurons. Analyses of crude neocortical membranes showed that HGF-induced *MET* autophosphorylation peaks during synaptogenesis. There is rapid HGF-induced phosphorylation of Met, ERK1/2, and Akt accompanied by two main morphological changes: increases in total dendritic growth and synapse density [6].

As the *MET* receptor tyrosine kinase has been associated with multiple neurodevelopmental processes [7], the consequences of disruptions in *MET* function differ according to cell context. For instance, in the forebrain, a risk allele for ASD in the *MET* promoter, which reduces *MET* transcript and protein concentrations [8], is associ-

ated with changed circuit function in typical and ASD human populations [9].

Upon binding to its receptor, HGF elicits relevant biological activities, including cell motility, division, survival, and differentiation [10]. *MET* is expressed in neuronal precursors and contributes to the development of the nervous system. Moreover, HGF or *MET* signaling ablation affects the “wiring” of the nervous system, leads to reduced survival of neurons, and decreases axon bundling of certain motor nerves [11]. Many studies showed that HGF is neurotrophic for embryonic cortical neurons cultured in vitro. HGF increases the number of hippocampal neurons and the length of their dendrites [12]. Specific neurotrophic effects of HGF have been reported on dopaminergic mesencephalic neurons [13].

ASD is linked with deficits in the ontogeny of neural circuits [14]. Moreover, the transcription of the human *MET* gene can also be regulated by FOXP2 and MeCP2, which are both factors that affect ASD-related circuit development in humans [15]. The association between *MET* and ASD is supported by the fact that cMet is expressed in brain areas in higher levels of cognition, executive functions, and language skills [16]. Because of the vital role of HGF-cMet signaling in normal brain development, including neurogenesis, synapse formation, and spatial learning function of the brain's hippocampal region, we aimed to study the HGF and soluble cMet serum levels in children with different stages of ASD.

Materials and Methods

In this case and control study, the blood samples were collected from July 2018 to March 2019 from ASD patients referred to Pediatric Neurology Clinic, 17 Shahri-var Hospital, Rasht, Iran. The diagnosis was confirmed at the clinic according to the criteria established in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The diagnostic criteria exist on a continuum of

severity and functional impairment. The disease severity was divided into three levels: level 1 = mild, requiring support; level 2 = moderate, requiring substantial support, and level; 3 = severe, requiring very substantial support (American Psychiatric Association, 2013). A total of 189 patients with ASD were enrolled in this study. ASD children on medication that address behavior/focus/attention during the previous six months, any food or drug allergy, use of any nutritional supplements during the last six months were excluded from this study. Also, patients with atypical forms of ASD, such as Rett syndrome, invasive developmental disorders without further specification, fragile X syndrome, Asperger syndrome, and Down syndrome, were excluded. The control group consisted of children with no clinical characteristics of ASD. They attended routine blood tests (e.g., periodic control exams, preoperative exams). All parents and guardians, regardless of child's age, signed the consent form.

Blood serums

Experimental and control serums were morning draws, frozen at -70°C immediately after collection and serum separation, until thawed for use in enzyme-linked immunosorbent assay (ELISA). All samples were assessed using commercially available ELISA kits (Human HGF ELISA kit [ab100534]) for HGF and human s-cMet ELISA kit (Catalog No. KHO2031) (Invitrogen, Corporation Camarillo, CA) for s-cMet, according to the manufacturer's instructions.

Statistical analysis

For statistical analysis, the values were compared by 1-way ANOVA using SPSS software, version 19, and the data were presented as Mean \pm SD. $P < 0.05$ was regarded as statistically significant.

Results

HGF serum levels in different stages of ASD and controls

A total of 189 patients (128 boys and 60 girls) with ASD (mild, $n=69$; moderate, $n=63$; and severe, $n=57$) (9.2 ± 2.3 years) and 82 healthy control (56 boys and 34 girls) (8.9 ± 4.1 years) were enrolled in this study ($P > 0.05$ for both sex and age between two groups).

The Mean \pm SD serum HGF concentrations were 239 ± 52.02 pg/mL in the ASD patients and 360.04 ± 71.15 pg/mL in the control group. A significant decrease in

HGF serum concentration was seen in the ASD group compared to control subjects ($P=0.004$) (Figure 1).

We have also measured HGF serum concentration in different stages of ASD. The serum Mean \pm SD concentrations of HGF in mild, moderate, and severe ASD groups were 297.54 ± 69.82 , 232.81 ± 56.41 , and 189 ± 33.25 ng/mL, respectively, while it was 360.18 ± 57.40 in the control group. These results showed that HGF serum concentration is significantly decreased in patients with ASD compared to the control group ($P < 0.05$) (Figure 2). Moreover, statistical analysis showed a significant difference between the three groups of ASD (P -values are shown in Figure 2).

Soluble MET serum levels in different stages of ASD and controls

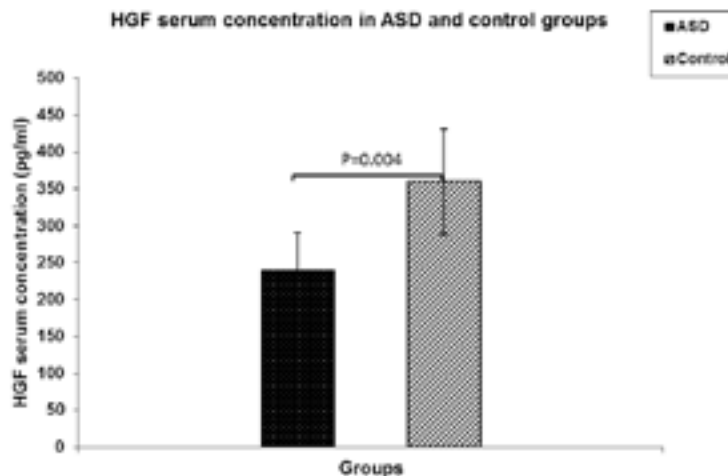
We have also measured serum levels of sMet by ELISA. The Mean \pm SD sMet serum concentration in ASD patients was 143.54 ± 32.50 pg/mL compared with the control group, which was 200.25 ± 31.16 pg/mL. A significant decrease in sMet serum concentration was seen in the ASD group compared to control subjects ($P=0.005$) (Figure 3).

We have also measured sMet serum concentration in different stages of ASD. The Mean \pm SD serum concentrations of sMet in mild, moderate, and severe ASD groups were 172.81 ± 37.69 , 129.81 ± 45.55 , and 85.18 ± 22.95 ng/mL, respectively, while it was 214.54 ± 34.17 in controls. Significantly decreased serum sMet concentration was seen in three ASD groups as compared to controls ($P < 0.05$) and is positively correlated with disease severity (Figure 4). Moreover, statistical analysis showed a significant difference between the three groups of ASD (P -values are shown in Figure 4).

Discussion

We studied the HGF and soluble cMet (s-cMet) serum levels in children with different stages of ASD. Our results showed both HGF and s-cMet significantly decreased in ASD patients compared with the controls ($P < 0.05$). We have also measured HGF and cMet serum concentration in different stages of ASD. The results showed that lower HGF and cMet serum concentration is negatively correlated with disease severity.

Growth factors, including HGF, have a crucial role in neurogenesis, synaptogenesis, and brain remodeling through neuron development, differentiation, and survival [6, 17]. Recent evidence shows that changes in the expression level of growth factors during embryogen-



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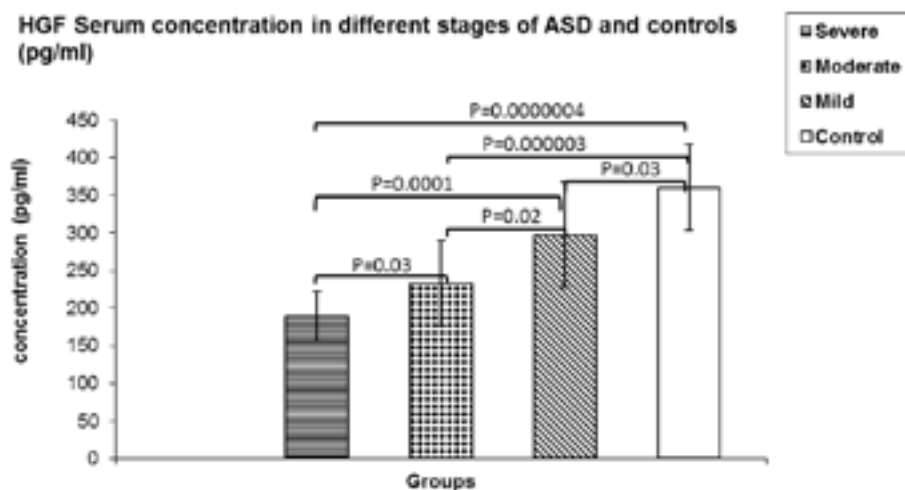
Figure 1. Hepatocyte Growth Factor (HGF) serum concentrations in the Autism Spectrum Disorder (ASD) patients and control group

esis are linked to the pathophysiology and clinical manifestations of attention-deficit/hyperactivity disorder and ASD [18]. Changes in the expression of *MET* in ASD patients suggest dysregulation of signaling that may contribute to altered circuit formation and function in ASD. The complement of genes that encode proteins involved in *MET* activation appears to undergo long-term compensatory changes in expression that may be a hallmark contribution to the pathophysiology of ASD [8].

Sugihara et al. studied the serum level of HGF in 17 male adults with high-functioning autism and age-matched 18 healthy male subjects by ELISA and showed significant change in HGF serum level in ASD patients compared to controls. They suggested that changed HGF expression may play a role in the pathophysiology of ASD [19].

Russo et al. (2009) showed that ASD children with severe gastrointestinal (GI) disease had significantly lower serum concentrations of HGF than controls. They suggested a relationship between HGF serum levels and the presence of GI disease in ASD patients and explained a possible functional role of the *MET* gene and ASD. They also suggested that the concentration of serum HGF may be a valuable biomarker for ASD patients, especially those with severe GI disease [20].

It has been documented that *MET* activation induces an alignment of presynaptic and postsynaptic elements that are essential for the assembly and formation of functional synapses by subsets of neocortical neurons that express *MET* receptors [4]. It has been shown that there is an association between reduced phosphorylated Akt and selected symptom severity in ASD patients so that Akt



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Figure 2. Comparing Hepatocyte Growth Factor (HGF) serum concentrations in different stages of Autism Spectrum Disorder (ASD) and the control group

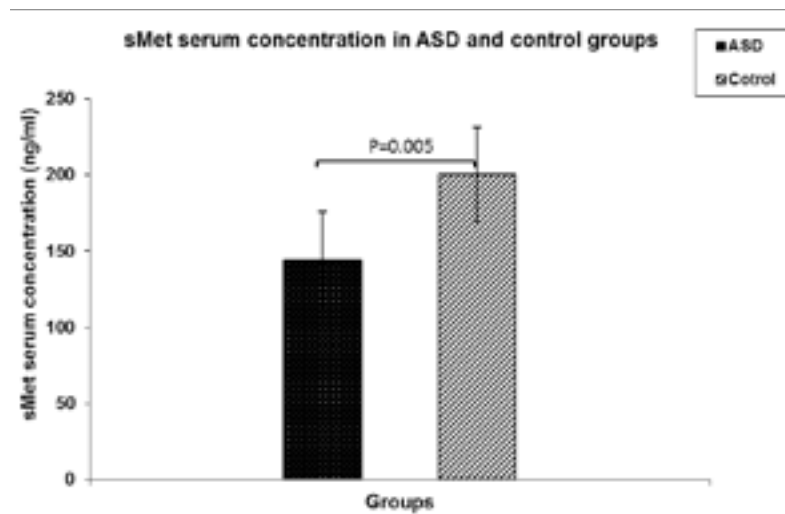


Figure 3. sMet serum concentration in the Autism Spectrum Disorder (ASD) patients and control group

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pathways may be related to the etiology of ASD [21]. Zhou et al. showed that the concentration of HGF increases in Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS) and is positively correlated with the severity of OSAHS. They suggested that determining the concentration of HGF in serum is essential for evaluating the severity of OSAHS and the degree of vascular endothelial dysfunction and assessing the risk of cardiovascular disease [22]. It has been shown that there is no significant change in serum HGF of patients with Parkinson Disease (PD). However, HGF level in Cerebrospinal Fluid (CSF) was higher in patients with PD than in controls. This result shows that HGF may play an important role in the pathophysiology of PD [23]. Liao et al. suggested that detecting serum HGF levels in patients with OSAHS has a certain clinical value in judging the condition, the curative effect, and evaluating the cardiovascular dam-

age [24]. It has been shown that increased serum HGF levels are related to carotid atherosclerosis, independent of known risk factors for atherosclerosis [25].

It has been suggested that there is a significant association between HGF gene polymorphism and its serum levels with ASD in an Iranian population and suggested that TT genotype may be linked to a decrease in HGF circulation levels in ASD [26]. Khoshdel Rad et al. showed that soluble cMet is a constant component of human serum and Cerebrospinal Fluid (CSF), and it can be used to diagnose meningitis [27]. It was shown that the serum level of s-cMet in the patients with various stages of Prostate Cancer (PCa) is significantly increased compared to normal controls and suggested that s-cMet might be involved in the pathophysiology of PCa and the progression of PCa [28]. It has been demonstrated that human Peritoneal

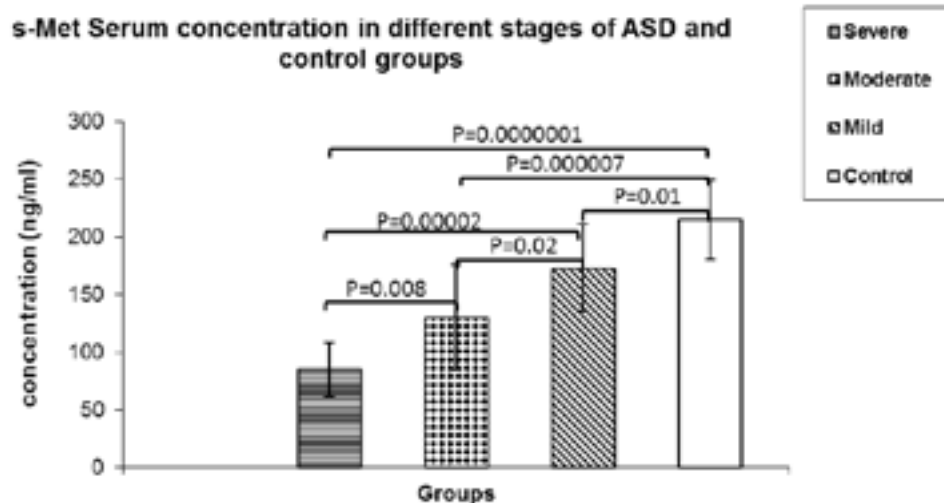


Figure 4. Comparing sMet serum concentrations in different stages of Autism Spectrum Disorder (ASD) and the control group

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Fluid (PF) and serum samples present sMet expression, while, starting from stages I to IV endometriosis, a significant increase of sMet concentration is observed compared to controls. This study shows that a high expression of sMet is correlated with advanced stages of endometriosis. They also concluded that detecting serum and PF sMet may help classify endometriosis [29]. It has been shown that serum concentration of HGF in cerebral infarct patients on admission was higher than in controls [30]. It was shown that HGF could induce the shedding of *MET* [31]. Thus elevation in sMet levels in the serum of patients with ASD may result from the elevation of HGF.

Conclusion

The study result suggests that serum HGF and sMet concentrations may provide a reliable and practical indicator of ASD and are negatively associated with disease severity. It is also concluded that HGF-Met signaling might be involved in the pathophysiology of ASD, and the detection of serum HGF and sMet may be useful in classifying ASD.

Ethical Considerations

Compliance with ethical guidelines

The study was approved by the Ethical Committee of the University of Guilan (Code: 1397-11065). All study procedures were done in compliance with the ethical guidelines of the 2013 Declaration of Helsinki.

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Authors contributions

Conceptualization and supervision: Soheila Talesh Sasani and Farhad Mashayekhi; Methodology: Somayeh Shabani; Investigation, data analysis, writing the original draft, review, and editing: Somayeh Shabani, Soheila Talesh Sasani, and Farhad Mashayekhi; Data collection: Somayeh Shabani and Soheila Talesh Sasani; Funding acquisition and resources: Soheila Talesh Sasani, and Farhad Mashayekhi.

Conflict of interest

The authors declared no conflict of interest.

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