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Attention Deficit Hyperactivity Disorder; Genotype-Phenotype Correlates

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Short Communication

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Abstract

Attention deficit hyperactivity disorder (ADHD) is one of the prevalent neurodevelopmental disorders that starts early in life and have long term impact on all life aspects of the sufferer; academically, socially, psychologically, and occupationally. Accordingly, understanding its multifactorial origin with its correlation to its manifestations and diagnostic criteria is crucial for individualizing the management plan for each case in order to get the best outcome and improve his/her quality of life. This short communication is summarizing the results of some of our researches investigating the genotypic phenotypic profile of ADHD in samples of Egyptian children.

Keywords: Attention Deficit Hyperactivity Disorder; Gene Polymorphism; Dopaminergic System; Folate Metabolism; DRD2 Taq1A Polymorphism; MTHFR Gene Polymorphism

Abbreviations: ADHD: Attention Deficit Hyperactivity Disorder; CAMP: Cyclic Adenosine Monophosphate; MTHFR: Methylene Tetra Hydro Folate Reductase.

Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that is characterized by a triad of inattentiveness, hyperactivity, and or impulsivity in a disturbing way that is not appropriate for the chronological age or the developmental status of a child or an adolescent [1,2]. It has a multifactorial origin in which the exposure to hazardous environmental risk factors interacts with the genetic susceptibility to produce its characteristic phenotype [3].

Psychophenotypic Profile of ADHD in an Egyptian Sample

We investigated the psychophenotypic profile of 80 Egyptian cases with attention deficit hyperactivity disorder (ADHD) according to DSM 5 diagnostic criteria [4]. They have been selected sequentially from cases under regular follow up at Child and Adolescent Psychiatry Clinic, Children's Hospital, Ain Shams University. Their ages ranged between 4 and 12 years with male to female ratio of 6.14:1 (86% males and 14% females). Parental consanguinity was reported in 25% of the studied sample while positive family history of neurodevelopmental disorders was detected in 12%. On the other hand, 22% had suffered from hypoxic perinatal insults [5].

ADHD was predominantly combined (inattentive and hyperactive) in 10% and inattentive in 90% of enrolled cases. According to Conner's Parental Scale 70% had severe type of ADHD while 25% and 5% had moderate and mild symptomatology respectively [5].

Reported comorbidity included delayed language development in 30% with stuttering in 9%, sleep disorders in 16% (insomnia, nightmares, and somnamulism in 9%, 4%, and 3% respectively), delayed bladder control (15%), pica (2%), and polyphagia (2%). Poor scolastic achievement was a major complaint in 95% with dysgraphia in 18% and dyslexia in 15%. Meanwhile violent behavior was reported in 12% and conduct disorder in 5%. We concluded that ADHD could present with a wide variety of phenotypic manifestations that necessitate thorough professional assessment to individualize the management plan for each patient in order to achieve the best outcome [5].

Dopaminergic System Genetic Polymorphism and ADHD

Accumulated evidence suggested that genetic polymorhisms involved in dopaminergic functioning may play a role in the development of inattentiveness [6]. Furthermore, molecular psychiatry studies showed increased frequency of polymorphism of candidate genes of the dopaminergic system comparing hyperkinetic cases with controls [7]. Such findings were supported by the fast symptomatic relief of hyperactivity and improvement of cognitive motivation and interest associated with elevation of the extracellular dopamine levels after using psychostimulants in 70% of the sufferers [6-8].

The Dopamine Receptor D2 (DRD2) Taq1A polymorphism affects the intercellular concentration of the second messenger cyclic adenosine monophosphate (cAMP) [8], so we explored the potential association between it and ADHD phenotype in 50 Egyptian cases compared to 50 controls. We found a significant association between ADHD phenotype and the prevalent distribution of A1 allele of the studied gene compared to controls who showed more prevalent A2 allele. Also, a significant prevalent association was documented between ADHD phenotype and the heterozygous A1A2 genotype distribution. On the other hand, ADHD phenotype showed a significant lower distribution of the homozygous A2A2 genotype [9].

Methylenetetrahydrofolate Reductase (MTHFR) Gene Polymorphism and ADHD

Maternal folate deficiency during gestation was reported to be associated with future childhood hyperactivity [10]. Low folate level affects neural stem cell proliferation, decreases apoptosis, and alters DNA biosynthesis [11]. In general, deficient maternal nutrients has been associated with increased risk of developing different neurodevelopmental disorders including autism spectrum disorder and ADHD [10].

Methylenetetrahydrofolate reductase (MTHFR) is crucial for folate chemical reactions as it helps converting folate to other metabolites for cellular processes. MTHFR gene polymorphism C677T and A1298C affect nucleotide synthesis and DNA methylation [12]. Several studies link folate/homocysteine levels with cognitive functions as patients with folate deficiency in their CNS exhibited cognitive deficits [13]. MTHFR gene is also a key regulator for folate versus homocysteine levels [14].

Accordingly, we investigated the association between MTHFR gene polymorphism and ADHD phenotype in a group of Egyptian children. Our results showed heterozygous advantage (heterosis) regarding studied C677T allele genotype with significant prevalent association in controls compared to ADHD cases. On the other hand, the genotype distribution of A1298C allele was significantly more prevalent among ADHD cases compared to controls [15].

Conclusion

ADHD is a neurodevelopmental disorder that can be controlled by different therapeutic modalities including psychostimulants, cognitive behavior therapy, dietary intervention, and environmental restructuring. Hence, the importance of researches that explore the genotypic phenotypic correlates of such a disorder to offer our patients the best professional service that enable them to achieve their utmost biopsychosocial potential and enjoy a better quality of life.

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