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Editorial

Recent Findings and Controversies on ADHD Trajectories

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Background

Within a developmental epidemiology framework, longitudinal research on children diagnosed with ADHD has yielded evidence for diverse outcomes. Samples assessed have included clinical populations, cohorts in the community and comparison groups without the diagnosis. These studies have shown that two thirds of cases continue having ADHD, but that core symptoms and subtypes may change with age.

ADHD has been considered a developmental disorder which could persist in adolescence and adulthood, whose age of onset had to be under 12 years, according to DSM-5. However, retrospective studies in subjects diagnosed with ADHD in adulthood reported that some had started symptoms in childhood, others in adolescence, and yet others in adulthood.

Adverse lifetime consequences of ADHD

Several follow up studies, such as the New York, Pittsburgh, Rochester Minnesota, Denmark and Sweden Longitudinal Studies have documented a high risk for adverse physical health, mortality, suicide, psychosocial, educational and mental outcomes in adolescence and adulthood [1-7]. In a meta-analysis, Erskine [8] compared outcome of ADHD and Conduct disorders, and concluded it was difficult to attribute adverse outcomes to either diagnosis, due to high comorbidity.

Differences between persistent and remitted cases

Findings have shown that persistent cases were at higher risk of having Oppositional Defiant, Anxiety and Addictive Disorders; social, educational, emotional and cognitive difficulties and family psychopathology. It was not possible to determine if differences were cause, consequence or due to association with a third factor. Meta analysis of studies on childhood predictors of persistence reported severity of ADHD symptoms, ADHD treatment, and comorbid conduct or depressive disorders [9,10].

Follow up of the MTA study, compared persisters and remitters, on a wide range of factors evaluated in childhood. Three logistic regressions were done, controlling for symptom severity and established cutoff points for definition of persistence. Risk predictors for ADHD persistence were: severity of childhood symptoms, comorbidities and parental mental health problems [11]. Functional evaluation of persistent, remitted ADHD cases and controls on emotional lability, neuroticism, Anxiety, Mood disorders and drug abuse; reported higher performance in controls, poor in persistent cases, and intermediate in remitters. They concluded that persistence vs. remission of symptoms can influence functional outcome [12].

Persistence of childhood ADHD vs. adult onset

Follow up of children from the Dunedin, New Zealand cohort [13] performed evaluation every two years from 3 to 38 years of age. Information was combined with retrospective reports from subjects diagnosed in adulthood, fulfilling or not the DSM-5 criteria for onset in childhood. Results were surprising, as only 5% of the diagnosed children persisted in adulthood, representing only 10% of the adult diagnosed sample. Several differences were found comparing both groups with controls.

Adults with persisting childhood ADHD diagnosis	Diagnosed with ADHD in adulthood
Male preponderance	No gender differences
Persisting cognitive deficits	Very few deficits. Personality disorders, drug and alcohol dependence
High polygenic risk	low
Educational, social, health, and judicial problems	financial problems

The authors concluded that an important group of adults fulfill DSM-5 criteria for ADHD, except for age of onset. They questioned the concept of adult ADHD being a continuation of childhood diagnosis. Discussion of these results argued that adults recall of symptoms could have sub-estimated childhood symptoms and over-estimated adult symptoms.

A longitudinal study of a twin cohort from England and Wales reported 21% persistence of childhood cases at 18 years of age, while 67,5% of those with ADHD at 18 did not have a childhood onset. Cases with childhood onset were influenced by perinatal factors, clinical features and certain aspects of family environment. Cases with onset at 18 years of age, were associated with clinical ADHD characteristics, impairment and psychiatric comorbidity. Persistent cases had more symptoms, lower I.Q., more functional impairment at home, school and friends, Generalized Anxiety Disorders, Conduct Disorders and Cannabis Dependence. Both persistent and remitted ADHD showed high male preponderance (72,5% and 66,7%) vs. adult onset, which had a similar male proportion as controls (44,6% and 44,2%). There were more women in the adult onset cases, but not more persistence. Several hypotheses for the differences found in adult vs. childhood onset were proposed by the authors

1. Subjects with adult onset could have the same predisposition to ADHD as the childhood onset cases, but it was masked by the presence of protective factors until life demands became greater.
2. Adult cases have a different disorder with symptoms similar to ADHD. However, when they excluded from the analysis those with comorbid anxiety, depression and cannabis dependence, 1/3 still had late onset.
3. Adult cases are a completely different disorder: more prevalent in women, less heritable. There was no difference if the twin had ADHD or not [14].

Effect of retarded brain maturation in ADHD outcome

A follow up of twins until 20 years of age in Sweden documented 10-14% of neurologic brain immaturity in childhood and adolescence, which was attenuated in adulthood. Influence of shared genetic factors was greater than non-shared environmental factors. They proposed the hypothesis that a delay in brain maturation could represent a factor for the outcome of ADHD in some children. This was supported by ENIGMA team in a neuroimaging study, where they found smaller volume in ADHD children in nucleus accumbens, amygdala, caudate and total brain volume than controls. Adolescents showed smaller hippocampal volumes up to 21 years of age. The IMAGE group from Vermont University reported a reduction in grey substance in ventromedial prefrontal cortex in children with dimensional ADHD symptoms and altered reaction time [15-17].

Genetic influences on outcome

Findings in this specific area are somewhat contradictory. The family genetic load is higher in persistent cases than in controls. Twin studies find additive genetic variance, while genomic studies find common risk alleles plus infrequent mutations. On the other hand, ADHD shares genetic vulnerability with other problems. The Psychiatric Genomic Consortium was able to determine a compound index of genetic risk for ADHD which can be used in future studies. The Avon Longitudinal Study of parents and children evaluated ADHD symptoms, accumulation of polygenic risk (RPG) from 7 to 14 years of age, assessing I.Q, social communication, pragmatic language and behavior. They identified four trajectories: low (82,6%), intermediate (7.7%), limited to childhood (5,8%) and persistent (3.9%). Subjects with persistent trajectories had higher polygenic risk index and higher multi-morbidity than the other groups. Findings were specific for ADHD and not for other disorders. ADHD with onset in adolescence did not have higher polygenic risk [18,19]. Epigenetic research reports that metilation at birth differentiated trajectories up to 7 years of age [20].

Critical review of DSM-5 age of onset criteria necessary for ADHD diagnosis

In order to ascertain if DSM-5 criteria for age of onset under 12 was confirmed, researchers from the Pelotas study in Brazil, followed a cohort from 11 years of age until they were 19 years old. Four groups were compared: childhood onset/no comorbidity-childhood onset with comorbidity-adult onset with and without comorbidity. Criteria for age of onset was excluded in the analysis. It was found that only 17.2% of children persisted with ADHD as adults while only 12.6% of adults had the childhood diagnosis. Results were not explained by comorbidity. The authors conclude that the diagnosis has scarce continuity and propose two syndromes with different trajectories [21].

Controversies on adult vs. childhood onset of ADHD

Possible explanations for the low prevalence of childhood onset in adult ADHD in the Dunedin, UK and Pelotas studies were discussed by other researchers and were replied by the authors:

1. Instruments used in evaluation missed inattentive cases. However, in the UK sample, inattentive symptoms had low representation in childhood as well. In New Zealand, the adult onset cases did not show the neuropsychological deficits typical of childhood onset. In Brazil, authors estimated that the instrument used in childhood could have missed 10% of children with inattentive subtype.
2. False positive paradox due to use of different informants at different times: parents in childhood and patients in adulthood. The later tend to under report early onset. This could have led to over estimation of adult onset ADHD and sub estimation of persistent cases.
3. The presence of subclinical symptoms and comorbidity in childhood. In New Zealand, teachers reported symptoms of ADHD and Conduct Disorder. In UK, symptoms of ADHD, Oppositional Defiant Disorder and Conduct Disorder.

It is possible that subclinical symptoms which are present in childhood, only add disability and reach complete diagnosis at later ages. This analysis supports the concept of ADHD as a developmental disorder and a dimensional continuum.

Finally, a paper published ahead of print studied the best way to define persistence and recommends a combination of reports from adults and parents and criteria of 4 symptoms. Using these parameters, 60% have persistent symptoms and 40% show disability [22-25].

Conflicts of Interest

The author has no conflicts of interest.

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