Transition of ADHD Patients from Childhood into Adulthood

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ABSTRACT

This article summarises the current knowledge base and cutting-edge research into ADHD as presented at the Medice symposium, 5th EUNETHYDIS International Conference on ADHD, 25 September 2018, Edinburgh, UK. The clinical perspective presents an overview of how ADHD symptoms change over an individual’s lifespan, the effects of comorbidity, and current treatment options. There is a high genetic correlation of ADHD with psychiatric disorders such as depression, signifying that ADHD is biologically determined and genetically driven. The neurobiological aspect provides insight into the genetic contribution to ADHD and the success of collaborative initiatives which serve to increase understanding into the genes and biological pathways involved.

Key words: ADHD; transition; clinical; lifespan; neurobiological; imaging

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INTRODUCTION

ADHD is a common disorder among children and adolescents; in 2007, global prevalence was reported to be 5.3%, although differences in methodology give rise to variable estimates.1, 2 Epidemiological prevalence is consistent among different countries although administrative prevalence and guideline recommendations for treatment can be inconsistent. Notably, the increase in diagnosis and treatment rates over the past three decades is likely due to improved public and clinical awareness with better access to treatment.2

In adults, ADHD has a pooled prevalence rate of 2.5% and studies support the view that at least two-thirds of young people with ADHD progress into adulthood with persistent symptoms of the disorder.3, 4 A gender variance exists with boys diagnosed more frequently than girls, although in adults the ratio of male to female patients with ADHD is approximately equal.1, 5

ADHD is a highly heritable disorder, and studies that investigate the disorder at the neurobiological level hope to provide some understanding of the mechanisms that drive persistence and remittance. Ultimately, such research is aimed at the development of biomarkers that can determine at an early age whether a child is susceptible to a highly persistent life course of ADHD.
THE CLINICAL PERSPECTIVE

Investigating ADHD across a lifespan is achievable when child and adult psychiatrists collaborate in research and clinical work, often developing a unique view on mental disorders from the life-term perspective. ADHD can be a persistent condition, and a meta-analysis of existing studies revealed that 15% of all patients featured full syndromatic persistence while 65% featured ongoing functional impairment.\(^{(6)}\) From a clinical viewpoint, the principal considerations are comorbidity and functional impairment.

Although the highest prevalence rates are observed in high-income countries, there may be environmental factors which negatively affect how adults cope with ADHD. However, the statistics from longitudinal and cross-sectional studies do not agree, and these discrepancies may be due to misdiagnoses of adult ADHD.\(^{(1, 5)}\) There have been investigations in persistence vs adult onset of ADHD where children who have not had ADHD have an onset in adolescence or adulthood, and although there may be convincing cases, careful assessment of an individual's psychiatric history and any substance use is required to avoid misdiagnosis.\(^{(7-9)}\)

If late onset of ADHD does exist, it is rare, and a study reports a figure of 0.3% for genuine late-onset patients in a sample of ~5000.\(^{(10)}\) For most neuropsychological variables, these individuals did not differ much from controls, and the only significant difference was in reading ability. However, there are many recognised trajectories of ADHD, and one interesting group are ‘subthreshold childhood-unrecognised ADHD’ individuals.\(^{(1)}\) Here, symptoms appear consistent throughout an individual's lifespan and above control levels. However, these symptoms are below the recognised diagnostic threshold for childhood ADHD, possibly explained through positive environmental influences and parental care. Given the lower diagnostic threshold for ADHD in adults combined with the higher demands of starting a family or a new job, many become symptomatic ADHD cases. It may also be that several adult-onset ADHD cases fall within this group.\(^{(11)}\)

Figure 1. Hypothetical trajectories of ADHD
Changes across a lifespan

Symptomatically, ADHD often changes over the course of an individual’s lifespan, especially since hyperactive symptoms tend to wane in adulthood. In addition, it is possible that people with ADHD—especially females—are not diagnosed as their symptom profile is mainly characterized by inattention symptoms, which are more difficult to recognize than hyperactivity. Attention problems are mainly genetically driven, and mood fluctuations and irritability recognized as new symptoms. However, these are not yet included in the DSM as current opinion holds that these features do not differentiate ADHD from other psychiatric disorders.\(^\text{(12, 13)}\)

Sex distribution also changes throughout a lifespan. The ratio of male-to-female prevalence of ADHD is approximately 4:1 in childhood, reducing to around 1:1 in adulthood. One possible reason for the male preponderance of ADHD in childhood and adolescence, although unproven, is that girls may display inattentive subtypes which are more easily identified in adulthood from patient self-reporting.\(^\text{(14-16)}\)

A 33-year follow-up study revealed educational, economic, and social outcomes were worse for children and adults with ADHD. However, there is a problem with the controls used as the group consisted of 15.4% with an alcohol-related disorder, 5.1% with a substance-abuse disorder, and 11.8% had been incarcerated.\(^\text{(17)}\) More recently, information from approximately 4 million health insurance data points in an age group of 18-30 year olds revealed that ADHD patients have significantly more comorbidity with mental disorders, the severity of which increases with age.\(^\text{(18)}\) Patients in older age groups tend to visit a doctor due to symptoms of depression, alcohol addiction, or perhaps anxiety disorder, at which point ADHD is identified as a side diagnosis. However, we are aware that the disorder starts early in life and need to do more for these patients.

Economic burden, comorbidities, and treatment

The annual healthcare costs of ADHD per patient across the lifespan are considerably more for comorbid patients, and this is evident for hospital stays and costs related to prescribed antidepressants. Surprisingly, costs attributed to stimulants are much lower than expected and this is in direct contrast to public conception that stimulants are primary cost drivers. Occupational therapy is another rising cost across the lifespan which is not evidence-based in adulthood, an indication that perhaps a closer investigation of the real costs per ADHD patient is needed.\(^\text{(19)}\)

The most frequent comorbidities for women are stress-related disorders which are much more prevalent in women with ADHD. Within the 18-30 age group, the biggest percentage difference between female patients with ADHD and controls are found for substance use disorder; obesity, affective disorders, and neurotic disorders.\(^\text{(18)}\)

Regarding stimulant treatment, there is ongoing concern that the use of stimulants in children and adolescents can worsen or even cause substance abuse in adults. (Fig 2) On the contrary, results from several studies indicate there is no risk of drug abuse, or alcohol dependence or abuse, and major studies suggest that stimulant use not only reduces the risk of developing alcohol abuse but may also have protective effects, (HR, 0.7).\(^\text{(19-22)}\) ADHD patients also have an increased risk of obesity but limited empirical evidence exists on the short- and long-term effects of psychostimulants on weight in individuals with ADHD.\(^\text{(23)}\) Scandinavian studies show that stimulant treatment in the ADHD-positive population within the prison system had a positive effect on later criminal and aggressive behaviour. Children with ADHD and other psychiatric disorders such as OCD and ODD have a significantly higher risk of criminal behaviour in later life, and improvements in how ADHD is detected and treated would seem to be an achievable solution to improving criminal behaviour in a population.\(^\text{(24-28)}\)

![Figure 2. Stimulant treatment and substance use disorder](19-22)
Mortality rates

Statistics show increased numbers of traffic accidents for patients with ADHD, and typically, men have more traffic accidents and citations than women, but in the ADHD population, this tends to be normalised. Males, but not females with ADHD who received medication, had a 58% risk reduction (HR, 0.42) of serious accidents.\(^{(29, 30)}\) ADHD patients vs controls who were involved in traffic accidents are known to have higher levels of stress before the accident and were also more likely to experience stress in their current lives with more emotional events occurring before the accident.\(^{(31)}\) As ADHD patients are known to have more stress-related disorders and overall cope less well with stress, this may affect their ability to concentrate, leading to accidents and other impulsive behaviours.

Suicide rates are also substantially increased in patients with ADHD, even after adjusting for psychiatric comorbidities. (Table 1) The risk is strikingly high in ADHD patients for both attempted and completed suicide, and stimulant treatment could reduce that risk considerably.\(^{(32, 33)}\) Accidents and suicides are, therefore, major causes of increased mortality rates in ADHD patients, and more noticeably, mortality rates increase in line with late ADHD diagnosis.\(^{(34)}\) To chart ADHD across the lifespan, we must acknowledge increased rates of mortality within these patients. Most phenotypes can be significantly reduced by stimulant treatment providing a markedly improved outcome, but how we achieve this is a major question.\(^{(6, 35)}\)

**Table 1. Attempted and Completed Suicide Odds Ratios (OR) Among Probands With ADHD Compared With Matched Control Participants\(^{(32)}\)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No.</th>
<th>Probands With ADHD</th>
<th>Control Participants</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted for SES</th>
<th>Adjusted for Psychiatric Comorbidities*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attempted suicide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>51 707</td>
<td>258 535</td>
<td></td>
<td>8.46 (8.07-8.87)</td>
<td>8.26 (7.87-8.66)</td>
<td>3.62 (3.29-3.98)</td>
</tr>
<tr>
<td>Male</td>
<td>36 102</td>
<td>180 510</td>
<td></td>
<td>7.12 (6.68-7.59)</td>
<td>6.88 (6.45-7.34)</td>
<td>2.93 (2.60-3.29)</td>
</tr>
<tr>
<td>Female</td>
<td>15 605</td>
<td>78 025</td>
<td></td>
<td>10.39 (9.67-11.15)</td>
<td>10.22 (9.51-10.98)</td>
<td>5.41 (4.60-6.36)</td>
</tr>
<tr>
<td>Completed suicide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>51 707</td>
<td>258 535</td>
<td></td>
<td>12.22 (8.67-17.22)</td>
<td>12.33 (8.73-17.42)</td>
<td>5.91 (2.45-14.27)</td>
</tr>
<tr>
<td>Male</td>
<td>36 102</td>
<td>180 510</td>
<td></td>
<td>10.32 (7.04-15.12)</td>
<td>10.37 (7.05-15.25)</td>
<td>3.70 (1.38-9.95)</td>
</tr>
<tr>
<td>Female</td>
<td>15 605</td>
<td>78 025</td>
<td></td>
<td>22.76 (10.06-51.50)</td>
<td>23.23 (10.22-52.78)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Transition

The emphasis is on the planned transition of mental health services, not the biological transition from adolescence to adulthood and evaluation of patients who underwent transition reported a poor experience.\(^{(36)}\) These patients have highly prevalent disorders and account for 2-5% of the population, yet we still have this dramatically poor transition from adolescence to adulthood. The problem may involve structural issues and the situation in the United States or in the UK is perhaps quite different from that in Germany, Switzerland, Norway, or France. It may be necessary to look for structural solutions for each and every country on an individual level, while adhering to general principles common to all.

There is evidence of a rapid decline in the use of mental health services for DSM-IV disorders after patients enter adulthood, at which point they tend to drop out of the system.\(^{(27)}\) Evidence from health insurance data reveals a consistent decrease in prescription stimulants in the 18-30 age group for both male and female patients. However, these patients re-enter the system again in later life, and they may have benefited with more continuous treatment.\(^{(31, 38)}\) Approximately half of all patients drop out of the system,\(^{(39)}\) including patients with neurodevelopmental disorders such as autism and ADHD, anxiety and depression, and incipient personality disorders.\(^{(36)}\) Most transition services tend to focus on patients with enduring axis-I disorders like schizophrenia, bipolar disorders, and eating disorders, as these patients need constant medication and automatically kept in the system.

For patients with ADHD, the main problems in transfer from childhood to adult mental health service provision include long waiting times along with changes in personnel, coupled with a limited number of specialised centres. In particular, a gap in age-appropriate services for patients between 18-25 years of age is evident, when individuals are neither adolescent nor fully adult and need special attention.\(^{(40)}\)
Recommendations for the successful transition of ADHD patients include the active transfer from childhood to adult mental health services on system persistence in the presence of comorbid disorders. The transition needs to be planned jointly between child and adult services as both sectors need to work together for this patient group. A suitable timepoint for transition might be when a patient leaves school, ideally between the ages of 18 and 19 years, as once they acquire independence it may be more difficult to keep in contact. There also needs to be adequate reimbursement schemes for both service groups with more education for patients and relatives on the relevant treatment changes on entering the adult mental health service system.\(^{(35)}\)

**THE NEUROBIOLOGICAL PERSPECTIVE**

ADHD is highly heritable, and the contribution of genetic factors to ADHD across the lifespan is complex; many genetic variants contribute to the disorder in most patients. There is evidence for both stability and change in the contribution of genetics to ADHD in childhood and adulthood, and we have some evidence for both quantitative and qualitative differences that may govern remission and persistence of ADHD in the transition from child to adult.

Genetic factors can explain approximately 74% of the ADHD phenotype,\(^{(41)}\) in both children and adults. However, there is no single gene which causes ADHD. Instead, ADHD is a multifactorial disorder of multiple, often hundreds, of common genetic variants. Individual ADHD patients show unique combinations of genetic variance.\(^{(42)}\) The liability threshold model which is used to explain the heritability of multifactorial disorders like ADHD, poses that individual genetic factors have a small effect, and only the combination of many risk factors, genetic and/or environmental, will cause disease onset.

If we study the relatives of ADHD patients, we find an increase in ADHD cases due to multiple genetic risk factors being transmitted through generations. (Fig 3) Through genome-wide association studies (GWAS), we can identify the common genetic variants relevant to complex disorders like ADHD. In these studies, we test millions of genetic variants across the entire genome for potential differences in frequency between cases and controls. However, >10,000 patients and a comparative number of controls are needed to identify the regions of the genome where genes associated with e.g., ADHD are present. Collecting such large samples of participants requires collaboration between researchers across the globe.

![Figure 3. Genetic transmission in complex disease.](image-url)
Since 2007, the Psychiatric Genomics Consortium (PGC) has brought the field of psychiatric genetics together, pooling data to obtain the necessary study power to identify genetic variants of importance.\(^{(43)}\) In ADHD, the Danish iPSYCH Consortium also added a large number of cases and controls in the collaborative studies. This collaboration has enabled the discovery of the first significant regions of the genome where we can find genes associated with ADHD.\(^{(44, 45)}\) Within this collaboration, and through GWAS, we expect to find a higher number of genetic risk factors, and data on polygenic risk scores show that individuals who carry many genetic risk factors have a much higher risk of ADHD than those who carry very few. These data are not enough for diagnostic purposes, but they are an excellent starting point to increase our understanding of the biology of ADHD.

Comparison of a study of ADHD symptoms in \(>17,000\) children from the general population with the results of the PGC/iPSYCH study of clinical cases has highlighted a very high genetic overlap, confirming genetic continuity between ADHD symptoms in the general population and the clinical disorder, with a genetic correlation of \(>96\%\).\(^{(46)}\)

The evidence for what occurs in the transition from childhood to adulthood in ADHD is not entirely consistent and makes it challenging to determine whether someone is likely to progress to have ADHD as an adult. Trajectories of ADHD symptoms from childhood to early adulthood show that individuals with a persistent trajectory have a higher burden of genetic risk factors (polygenic risk score; PRS) for ADHD, and this finding was specific for ADHD genetic burden; a PRS for schizophrenia showed no association with ADHD symptom trajectories and supported the idea that we can distinguish remittance and persistence based on the number of ADHD-associated genetic variants a patient carries.\(^{(9)}\)

Where twins were studied, the genetic architecture of ADHD was found to change over the lifespan, suggesting that genetic risk factors must also change. Those that contributed to the heritability of ADHD at 8-9 years of age became less important as the child matured to a young adult, at which point other genetic factors became relevant and played a role in later stages of development.\(^{(13, 47-49)}\) We know that the brain changes during adolescence, and an investigation of the dopamine transporter gene (DAT1), a known gene for childhood ADHD, revealed a different allele being associated with childhood and adulthood ADHD, suggesting qualitative differences between the two groups.\(^{(50, 51)}\)

However, a GWAS meta-analysis on adult vs childhood ADHD revealed \(>80\\%\) of shared genetic risk factors; this overlap is higher than expected given the proposed changes in the genetic contribution over the lifespan.\(^{(52)}\) More research is needed to fully understand the contribution of genetics to the lifespan transition in ADHD. Gene-environment interactions are likely to be a factor, lack of power in the GWAS may be contributing, and investigations have found no genetic factors that distinguish patients with a persistent path of ADHD from those that remit.

**Transition and the brain**

Imaging studies in children with ADHD are of limited sample size, and we need replication in larger sample sizes. Brain mechanism studies confirm the involvement of the noradrenergic and dopaminergic systems in ADHD, and although many brain regions are implicated, inconsistency between studies is evident.\(^{(6)}\)(Fig 4) This conflict highlights the importance of combining studies and integrating knowledge by collaboration between researchers. In the ENIGMA (Enhancing Neuro Imaging Genetics through Meta-Analysis) Consortium’s ADHD Working Group,\(^{(53)}\) more than 40 different research groups are now working together to share protocols, and all summary statistics from individual analyses are collated for meta- and mega-analyses. Participation is vital to increase the sample size, and the majority of groups with imaging data already participate in ENIGMA ADHD, which can now work with data from 36 cohorts and over 4,500 cases and controls.
Transition of ADHD Patients from Childhood into Adulthood

Current Enigma ADHD projects

i) Analysis of subcortical volumes and the intracranial volume (ICV)

Results reveal the ICV and most subcortical regions to be somewhat smaller in patients with ADHD than in controls. Effect sizes are small, and not all patients show the same picture. In terms of age groups, we find that these volume reductions occur only in children, even though the adults in the studies all have clinical ADHD. Data plots demonstrate what appears to be delayed maturation of the brain in early years, which then catches up in adolescence, and achieves apparent parity (in structure at the level investigated) by adulthood.\(^{54}\) There are no data on ADHD in the elderly, and this is an area that warrants further research.

ii) Analysis of cortical thickness and cortical surface area

In the analysis of cortical thickness and cortical surface area data, the main difference between patients and controls appeared to be in the surface area of the brain cortex. Case-control differences are found in the fusiform gyrus and temporal pole regions but effect sizes are very small.\(^{55}\) Looking at those across the lifespan showed that all differences observed occurred in children. There appears to be no significant difference in adults, even though they have the clinical disorder. If differences between adults with and without ADHD are not present at the level of volume, surface area, or cortical thickness, could there be differences in brain connectivity, either structural or functional? Diffusion tensor imaging (DTI) studies have investigated white matter, structural connectivity within the brain in adults with ADHD, and have provided useful data on water diffusion, fractional anisotropy, and mean diffusivity, giving us valuable information on the integrity of white matter. Findings revealed significant differences adults with ADHD and controls, predominantly in the corpus callosum, corona radiata, and in thalamic radiation, suggesting there may be an altered myelination profile in the adult ADHD brain.\(^{56}\) However, these studies are still of relative limited sample size, and the field awaits analysis of the DTI data present in the ENIGMA ADHD Working Group.

A neglected region of the brain in ADHD research is the cerebellum, and recent investigations into growth trajectories of this region found differences in the cerebellar white matter, suggesting that structural connections in the cortex and cerebellum may play a role in ADHD. As in the subcortical and ICV study, reversal is also seen in late childhood into adulthood.\(^{57}\)
A recent review paper suggests that different brain mechanisms contribute to remission and persistence of ADHD across the lifespan. With evidence for three models that may apply to different regions of the brain, we may be able to distinguish patients destined for either path.\(^{(10)}\)

**CONCLUSION**

The transition between childhood and adult ADHD medical health services needs to be improved. We know that hyperactivity decreases while inattention becomes more relevant with age, and that factors such as severity, comorbid conditions, and socio-economic status also predict worse outcomes for patients. There are questions regarding adult onset of ADHD and male dominance in childhood ADHD, and the reason behind changing sex ratios has yet to be determined. Differences in brain anatomy, connectivity, and function in ADHD occur in a widespread manner, and in many studies, only children with ADHD have been investigated, with longitudinal data remaining scarce yet needed to draw firm conclusions. Different mechanisms may contribute to remission of ADHD across different brain regions; volumetric, cortical surface area, and thickness alterations seem to be attenuated in adulthood despite persistent ADHD diagnosis, while imaging studies show that white matter changes may still be present in this group.\(^{(11)}\)

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