Poverty, maltreatment and attention deficit hyperactivity disorder

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a common condition affecting many thousands of children. It is a condition that can have adverse health, social and educational outcomes. It also exacts significant societal costs, economically and socially. This paper hypothesises that the population of children receiving a clinical diagnosis of ADHD is aetiologically heterogeneous: that within this population, there is a group for whom the development of ADHD is largely genetically driven, and another who have a ‘phenocopy’ of ADHD as a result of very adverse early childhood experiences, with the prevalence of this phenocopy being heavily skewed towards populations living with poverty and violence. A third group will have a high genetic risk and have been exposed to violence. These groups will overlap, with epigenetic phenomena and other environmental factors, for example, preterm birth, poor intrauterine growth, foetal exposure to teratogens, playing an important role for all affected children in determining the severity of their functional difficulties.

BACKGROUND

Phenocopies

Phenocopies occur when people exhibit a phenotype that appears identical to that found in other individuals who have a linked genotype, but do not possess this genotype themselves. Environmental factors may cause this, as occurs in Rutter’s autism phenocopy described in Romanian orphans adopted by western families in the early 1990s.

Definition of ADHD

To paraphrase DSM-IV-R, ADHD is a condition comprising a degree of impulsivity and hyperactivity and/or inattention to a point that is disruptive and inappropriate for developmental level. It must be pervasive and been present for at least 6 months. There are two subtypes: inattentive and hyperactive/impulsive. The severe combined ADHD is also referred to as hyperactivity or hyperkinetic disorder. It is a dimensional disorder with assessment and diagnosis dependent on careful history taking, and observational assessment in more than one setting.

Aetiology of ADHD

It is well established that attention deficit hyperactivity disorder is a familial and highly heritable disorder.

This quote, from a recent review, firmly identifies genes as the primary aetiological factor leading to the disorder we recognise phenotypically as ADHD. A number of possible and probable specific susceptibility genes are now identified. However, genetic studies by their very nature are not representative of the general population because they either systematically or inadvertently exclude families who, for socioeconomic reasons, cannot or will not take part. This includes families with low literacy, high mobility, dysfunctionality and violence. For studies, as they do, relying on volunteers and requiring high levels of compliance and partnership, such families are unlikely to put themselves forward, and even if they do, are much more likely to drop out. It follows that children who have experienced maltreatment are highly under-represented in this body of research.

Another school of thought sees ADHD as a largely environmentally determined condition:

...The impact of the early environment on offspring phenotype is a central theme in the biological, social, and medical sciences. This is not least due to human evidence that major early life stress events markedly increase vulnerability for developmental and adulthood psychopathology, including post-traumatic stress disorder (PTSD), attention deficit hyperactivity disorder (ADHD), conduct disorders...

A third view is of ADHD as a diagnosis with a common endpoint but a variety of pathways leading to it.

AD-HKD (attention deficit—hyperkinetic disorder) is an aetiologically heterogeneous disorder that can be caused by a range of biological, psychological and social conditions that can act individually or together to increase the risk of AD-HKD.

Despite these three approaches to our understanding of the heterogeneity of the pathways leading to ADHD there is, with some outlying exceptions, a homogenous approach to management, drug treatment and research exploring an evidence base for these. If there are, in effect, distinct disorders with different aetiologies and different pathologies, with albeit similar symptoms, there may also be differences in the natural history of the problems presented and between what does and does not work in management, therapeutics and approaches to education.

IMPACT OF EXPOSURE TO CONFLICT AND VIOLENCE ON BRAIN DEVELOPMENT AND FUNCTION

The infant human brain at birth is relatively immature in comparison to other mammals. Consequently, the first two years of life, especially the first, see marked growth and development of the brain, including the establishment or loss of cellular interconnections and cell culling. The direction and pattern of these processes is partly genetically, partly environmentally driven although, of course, these factors are not independent. The emerging science of epigenetics is providing some explanation as to how they inter-relate. However they do, it does not alter the undeniable conclusion that our children’s brains are sculpted irrevocably by their early life experiences, and that these impacts last into adulthood.

There has emerged a large body of literature describing and explaining the impact of environmental violence on the developing brain (see Glaser for review). What this reveals is that children exposed to early violence display altered responses to confrontation and conflict; in essence they are ‘hard-wired’ to be anxious, distractible, highly aroused and impulsively aggressive in situations of conflict. This is largely irreversible.

These children present with hyperactivity, distractibility and impulsive aggression, and...
thus, it is easy to see how they might fulfil criteria for a diagnosis of ADHD.

Older children currently living with violence and fear are anxious, highly aroused, and have raised cortisone, as do younger children. Although for those older children experiencing violence later in their childhood raised cortisone does not have the same long-term impact on brain structure, fearful highly aroused children are also distractible, inattentive, overactive and impulsive. Weinstein et al explain their difficulties with attention and concentration as caused by a constant re-running of previous experiences of trauma—a form of post-traumatic stress disorder, presumably further exacerbated by anticipation of future trauma. They argue that the physical restlessness they display is a function of hyper-vigilance. This is another group who can fulfil criteria for a diagnosis of ADHD, although for these children recovery is possible if they attain a place of safety.

Of course many children have experienced early violence and continued to live with it throughout childhood, and so, suffer the early and late consequences of exposure to violence.

Genetic and epigenetic factors in ADHD

Gene–environment interactions were once conceptualised in two ways. In this context, that is, of neurodevelopmental problems, parents theoretically can transmit to their children an adverse environment and a genetic susceptibility to ADHD; on the other hand, a child with a specific genotype (and at risk of hyperactivity and impulsivity) may behave in ways that elicit maltreatment. Dopaminergic and serotonergic systems appear to be important in the aetiology of ADHD. A gene of potential interest is monoamine oxidase A (MAOA). Caspi et al found that children exposed to different severities of maltreatment did not differ in their MAOA activity, suggesting that in this case, genotype, and therefore, the resulting phenotype, did not influence a child’s risk of maltreatment.

Epigenetics provides another way of understanding how genes and environment interact in that there is increasing evidence that gene expression is modulated by the environment in which the organism grows and develops. Genetic information is encoded not just in DNA linear sequences but in epigenetic changes in chromatin structure such as DNA methylation or covalent modifications of the DNA-binding proteins. These alterations can change genetic expression, or even switch genes off, and may be part of the explanation of how maltreatment affects the developing brain. For example, the relationship between maltreatment and subsequent antisocial behaviour depends in part on MAOA genotype, with children with the low-activity alleles showing a stronger relationship between maltreatment and later antisocial behaviour than those with high-activity alleles. These studies suggest that these environmental variables could moderate the association between ADHD and MAOA, with children varying genetically in their susceptibility to the malign impact of violence on their development.

Recent work by Shalev et al has revealed that repeated exposure to violence during childhood is associated with telomere erosion which, although not specifically relevant to this paper, is a further illustration of the effect of violence on the genome.

Demography of violence

There is a higher prevalence of violence in low-income families, including sexual violence, domestic abuse and child maltreatment, which show marked socio-economic inequalities in prevalence and mirrored in steep gradients in abuse registration (figure 1). Gradients are even steeper for child abuse deaths—the rate for children in the UK between 1980 and 1995 in Social class V was 17 times that of children in Social class I. Poverty is associated with other environmental risk factors for overactivity, including low birth weight and prematurity, and intrauterine exposure to smoking and alcohol, although often such children may not achieve criteria for diagnosis. These factors are themselves linked to domestic abuse.

ADHD also shows a gradient across social classes. Indeed if all child populations in the UK had the same prevalence of ADHD as seen in the wealthiest quintile, we would have a 54% decrease in ADHD prevalence overall. Thus there is a very marked class bias in clinical ascertainment. The hypothesis presented here is that these social class differences reflect those in ADHD phenocopies.

TESTING THE HYPOTHESIS

If there are two, albeit overlapping, populations with ADHD, we would expect that if we study them carefully, we might find subtle differences in presentation or natural history. Is there evidence in the literature of difference between genetic and ‘environmental’ ADHD? In community studies from the USA, abused girls with a diagnosis of ADHD were more likely to be diagnosed earlier than were controls (ie, girls with a diagnosis of ADHD but no history of abuse). Abused children with ADHD have been found to have more severe impulsivity and inattention but less hyperactivity compared to non-abused children with ADHD. So although individual children from the two groups may be clinically indistinguishable, there are differences between them at a population level.

ADHD is commonly comorbid with conduct disorder (CD). This is a disorder whose aetiology, although complex, is very strongly associated with poverty, family dysfunction and child maltreatment. If this hypothesis is true, then the ADHD that is found comorbid with CD may also have its origins in maltreatment. This is supported by Szatmari’s work in Canada, which showed that family dysfunction and, for boys, service needs...
disappeared as significant variables associated with ADHD when comorbidity for other disorders were factored in, of which by far the most common was CD. Unsurprisingly, abused children with ADHD have poorer outcomes in adulthood, but that could have several alternative explanations as there are many confounders that could account for these differences in outcome.

PROBLEMS FOR DIAGNOSIS, MANAGEMENT AND RESEARCH

Diagnosis

For the clinicians faced with a child presenting with hyperactivity disorder in the context of a history of maltreatment, it is often extremely difficult to distinguish the child with ADHD and the child whose clinical presentation is a function of their adverse experiences. Further complexity is added by the common comorbidity of CD associated with hyperactivity. As seen, children growing up with abuse and violence have anxiety and attachment disorders, and fulfill list criteria for ADHD/HD without necessarily having primary hyperactivity disorder; this group of children also have high rates of CD itself highly skewed to poverty. Some children with primary hyperkinetic disorders will also be abused or subject to poor parenting, itself a risk factor for delinquency and for poor outcomes in ADHD (figure 2). Clinically this complex inter-relationship between abuse/poor parenting, ADHD and CD/delinquency is extremely challenging diagnostically. Children presenting with an ADHD phenotype tend to get the diagnosis regardless of aetiology, as if it is simply a disorder that children arrive at from many different directions, the implication being that the aetiology in each particular case is not important.

If one considers the guidelines on ADHD diagnosis from professional organisations in the USA, the water is no less muddy. The American Academy of Paediatrics’ ‘Evaluation of the Child with ADHD’ states:

The guideline is not intended for children ……who have experienced child abuse and sexual abuse. These children too may have ADHD, and this guideline may help clinicians in considering this diagnosis.

It does not state why the guideline is not intended for maltreated children, although the implication is that clinicians should be wary of making a diagnosis of ADHD in such cases. Nor does it explain how the guideline can help in discriminating what is certainly implied as two populations of similar children.

Management and therapeutics

One interesting question is do children in the proposed ‘phenocopy’ group respond differently to stimulants. Informal discussions with colleagues reveal shared experiences of children diagnosed with ADHD, but with very socially disadvantaged backgrounds, showing good initial but not sustained responses to stimulants, and thus, requiring ever higher doses of stimulants to control their behaviours. What does this mean for the evidence base for stimulants? If clinical trials have not distinguished between these groups, do we really have an evidence base for stimulant therapy for all children with a clinical diagnosis? This poses not just a diagnostic dilemma, but an ethical one, as we could be in danger of medicating children to maintain them in abusive environments in response to pressure from families, schools, social workers or youth offending teams for ever-increasing doses of stimulants.

There are also problems in relation to early intervention and parenting, for example, the Incredible Years programme, which, it is claimed, reduces ADHD severity. But who are the children in these studies? If the study populations are skewed to children exhibiting ADHD symptomatology as a result of adverse early life experiences, a not unreasonable supposition since these studies have tended to lump ADHD and CD together, what is being measured are interventions to improve the parenting capacity of parents whose parenting abilities are so poor that their children have been adversely affected. For those children who have a strong genetic susceptibility to ADHD, their parents may have a range of parenting skills and capacities and include many parents who are adequately, or even highly, skilled but nonetheless struggling with a very challenging child. Not only does a one-size-fits-all approach to early intervention imply that a child’s behaviour is, in part, a function of the parenting skills of all parents with an affected child (a situation somewhat analogous to that in the 1950s in which autism was blamed on refrigerator mothers), it may be denying the right type of parenting support to many parents.

Research

This hypothesis raises doubts about the validity of much research? To quote Stein, the lack of clarity in defining ADHD affects all past and current work. ADHD differs from many other conditions in that it lacks biological markers. To date, in the overwhelming majority of studies, ADHD remains a purely clinical label and the criteria for its diagnosis and for inclusion in studies are somewhat subjective.

We need to approach published research bearing this in mind and evaluate critically the population under study— who exactly are these children? Are the conclusions valid for all children with ADHD or a subset of them?

CONCLUSIONS

ADHD is a common condition, affecting between 3% and 5% of children, with important consequences for adverse long-term outcomes in health and education and welfare; as such it is an important
public health problem. It is also a significant problem among children affected by violence. Clinicians working in this area face difficult clinical and ethical dilemmas, which might be less challenging if our understanding of the population expressing this behavioural phenotype was better. We need research to robustly test the ADHD-phenocopy hypothesis, including genetic studies that incorporate, or control, epigenetic phenomena. Current whole population cohort studies are problematical because they rely on current diagnostic approaches. In addition, they often fail to adequately record exposure to violence, including to domestic abuse which, as is pointed out above, is itself associated with other confounding risk factors for ADHD, such as prematurity, maternal alcohol abuse, and maternal smoking; for example, domestic abuse is identified in the ALSPAC cohort by the parental question ‘Has anyone been cruel to you’, a question that renders this cohort unsuitable for any study investigating the impact of domestic abuse on children as it is likely to be very insensitive. Longitudinal family studies using cohorts from genetic studies may help, but they need to include qualitative as well as quantitative approaches, and include children’s experiences of school as well as at home. We need in addition to investigate whether children with ADHD who have a history of child maltreatment, including domestic abuse, respond differently to medication to children without a history of maltreatment and violence, and to review the effectiveness of drug treatments and other therapeutic approaches in these different groups.

This hypothesis has wider implications for the nature, implications and limitations of other diagnoses, which are based on symptoms alone, without biological markers, with the possibility of overlooked heterogeneity. A greater knowledge of epigenetics, which can be anticipated in the coming years, has huge potential to improve our understanding of the determinants of health and illness in children, and the interaction of social and biological drivers of diseases and disorders in childhood.

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