Medical Update on ADHD

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Realising possibilities

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Quality of life in adult attention deficit hyperactivity disorder remains a priority and the ultimate aim in management. Agarwal et al. in their review article reinforce that quality of life has become (remains) an important measure of outcomes in both research and clinical settings. One of the questions they consider is: What is the impact of adult attention deficit hyperactivity disorder on quality of life? They further describe Quality of life (QoL) as a multidimensional construct that primarily concerns a patient’s personal evaluation of his or her life with regard to global health, handicaps or impairments, and daily living activities. They review a number of scales that have been utilised in an attempt to measure and objectively quantify the QoL in adult ADHD. Finally they conclude as can be expected that attention deficit hyperactivity disorder to significantly worsen the quality of life in adults.

It is thus appropriate in the first article for Dr Rykie Liebenberg to review the very important question of ADHD and Driving. Although this topic has not received extensive research, a definite negative link between ADHD and driving has been shown. An alarming finding has been that teenagers with ADHD showed a higher risk (36%) for crashes as well as a higher incidence of traumatic brain injury due to amongst others inattention while driving cars. The most important findings have been a reduction in driving incidents where ADHD patients received treatment. Various studies reported improved driving skills on medication e.g. reduced driving errors (due to improved attention, better self-control and faster to startle events). In the UK it is mandatory to declare ADHD when applying for a driving license. Should this be done in South Africa as well to improve our exceptionally high accident rate and road deaths?

The second article by Dr Eleanor Holzapfel explores the concept of cognitive dysfunction in ADHD. Although multiple cognitive domains are affected by ADHD, executive function appears to be an umbrella for various complex cognitive processes. She further explains that executive function provides the mental skills that enable a person to successfully engage in goal-directed, independent, autonomous, efficient and socially adapted behaviours. After exploring the neuroanatomy of executive function the many neurological and psychiatric disorders that involve impaired executive function is mentioned. Typical examples of executive function include: cognitive flexibility, working memory, temporal information processing, response inhibition, planning and organising, task inhibition and self-monitoring and regulation. Ultimately once again cognitive deficits can severely compromise social and occupational functioning, psychological development, mental health as well as quality of life and require active intervention.

The last article by Dr Rassie Erasmus reports on the association between ADHD and allergic disease. This topic whether rooted in comorbidity or causality has been of interest for many years. It is known that children with ADHD have a high risk of developing allergic diseases. Allergic sensitisation is an important risk factor for the development of allergic diseases. The prevention of allergic sensitisation might thus be important in decreasing the burden of ADHD. Dr Erasmus reviews several studies related allergic disease e.g. asthma, allergic rhinitis, atopic dermatitis, allergic conjunctivitis and food allergies as well as aspects of growth patterns, use of medications to manage allergic conditions as well as the role of poverty. The conclusion remains that these issues needs further research into the underlying neuro-biological and immunological mechanisms.

We thank these three authors for their further exploration into the consequences and nature of ADHD.

References
I have been walking to work lately, and observing driving behaviour from a different angle. I also have time to think about what I observe, including the colour of the purple Jacaranda flowers and the smell of the star jasmine along the way, and I realised how badly a lot of people drive. I have nearly been run over a number of times, and I count the number of traffic violations I see very day. In two kilometres, it is at least seven to ten illegal activities per day.

The thought crossed my mind, that if one considers the core diagnostic features of ADHD, namely inattention, impulsivity/hyperactivity as well as emotional dysregulation, most of the drivers on the road would be classified as having quite a serious problem. I would go as far as to state that they should be considered unfit to drive and a risk to themselves and others. I have had the urge to stock up with some methylphenidate and pass it out as I walk.

But in reality, of course, not everybody who drives badly has ADHD. However, we do know that the condition affects driving adversely. Not so long ago, ADHD was considered a childhood disorder that was outgrown by puberty, so driving was never an issue, nor substance abuse to any significant extent. (Weiss et al. J. Psych Pract, 2002). This has changed, and we know that 4.4% of the adult population has ADHD, and only about 17% receives treatment. (WHO epidemiological study). The chances are good therefore, that quite a number of drivers on the roads of the world have some degree of inattention, impulsivity and emotional dysregulation, enough to satisfy criteria for ADHD.

Executive dysfunction is responsible for many of the dysfunctions in ADHD, and would by its very nature influence driving. Inhibition is a very important frontal lobe function that is impaired in ADHD, and would be potentially very dangerous on the road, while driving a two ton killing machine called an automobile. Rage outbursts are present in about 90% of patients with ADHD, and that is also a dangerous, and unfortunately, common occurrence in South Africa.

It seems tempting to say it doesn’t matter, but some studies seem to show that the effects are far reaching and devastating for the individuals concerned, as well as for the economy.

We know from research done in the South African context, by Dr. Renata Schoeman, that the medical costs for ADHD sufferers are seven times higher than in the normal population. This includes visits to the emergency room, accidents and trauma.

It also brings into focus the other big difference between adults and children with ADHD, which is the high incidence of comorbidity. The important condition that would affect driving would be substance abuse, probably with alcohol intoxication at the top of the list. The comorbid incidence of alcohol abuse in ADHD is about 27%, with other substances at 18%. The incidence of alcohol abuse is significantly increased in non-medicated patients.

In South Africa we have one of the highest accident rates in the world, and the aggression on our roads is probably unmatched in the world. In June 2017, the AA released new data on road fatalities in South Africa for 2016. They showed an alarming jump in deaths on local roads, and recorded the highest number of road deaths in the past ten years. Human factors are indicated as the biggest contributor to road crashes and fatalities, accounting for 77.5%: Vehicle factors (6%) and environmental factors(16.5%) make up the balance.

The human factors are (The comments in parentheses are my own):
• Jaywalking (impulsivity, no delayed gratification, inattention)
• Hit and run crashes: (impulsivity, no thought for consequences)
• High Speed (impulsivity, inattention, time blindness)
• Overtaking in the face of oncoming traffic (impulsivity)
• Drunk driving, or driving on drugs (substance abuse)
• Fatigue (poor planning, time management)

South Africa is 42nd in the world when it comes to road deaths, but has the highest prevalence of road deaths associated with alcohol abuse. Johannesburg ranks as the 13th most likely place in the world to die on the road. The economic cost is huge, estimated to be R142.95 billion in 2015, which equates to 3.4% of GDP, as compared to 2.2% of GDP in similar countries. The indirect cost to the economy will be even bigger.

There are no local studies on driving and ADHD, and not that many anywhere. Some studies have shown the following:
• Driving without a license : X 3 in ADHD
• License suspended : X 8
• Repeated violations : X 3
• Driving while impaired : X 20
• Experiencing a motor vehicle accident (MVA) : X 2-4
• Being at fault : X 4
• Multiple MVA's : X 7
• Suffer bodily injuries form MVAs : X 3
A study from Taiwan tracked teens with ADHD for two years and showed a higher incidence of traumatic brain injury, compared to controls. It might be due to inattention while driving cars or bikes, or reckless behaviour.

“Impulsivity is very much linked with risky health behaviours.”

Dr. Chen, Taipei Veterans General Hospital in Taiwan

Another study done in Stockholm, by a team led by Zheng Chang PhD, found men with ADHD had a 38% lower risk of having a MVA in months where they received medication vs months when they did not receive medication. Women had a 42% lower risk.

The researchers estimated that more than 20% of MVAs involving patients with ADHD, could have been avoided had the patients been taking medication during the entire follow-up.

“The association between ADHD and MVCs (motor vehicle collisions) is driven by the core symptoms of ADHD - inattention, hyperactivity and impulsivity - as well as by problems that frequently co-occur with ADHD, such as excessive risk taking, poor control of aggression, and substance use.”

Dr. Chang

Study published online in May 2017, JAMA psychiatry

Dr. Thomas Power, director of the Centre for Management of ADHD at Children’s Hospital of Philadelphia, published a study in 2017 with his colleagues, on the crash risk of young drivers with ADHD. They reported the risk as elevated, but not as high as previous studies have reported. The showed an increased risk of 36%, and not the 200-400% increased risk reported before. As a general rule, these researchers feel the risk is manageable in young drivers, but there is still reason for concern. There are subgroups where the concern is greater, including those with antisocial behaviour problems or substance use disorders. They suggest education, the use of medication, and getting professional help where needed.

A study from 2013 shows that teens with ADHD had significantly more variability in speed and lane position after being distracted in a driving simulator, than their peers without the disorder.

Another study, published in European Psychiatry in 2013, done in The University of Heidelberg in Mannheim, Germany, showed that daily use of atomoxetine for 12 weeks in adults with ADHD had significantly reduced driving errors in the categories of attention, self-control, and driver skills during a standardised traffic test, compared with participants with untreated ADHD. In addition, “self-reported critical traffic situations” decreased significantly at the endpoint for the treat group.

Dr Sobanski (lead author) says: “Studies that go beyond core ADHD symptoms and also investigate the impact of pharmacologic treatment on functional impairment are important.”

A study of 61 young adults with ADHD showed that those treated with lisdexamphetamine for 5 weeks reacted 9% faster to startle events and were 67% less likely to have a collision than those who received placebo.

A study done by Richard Merkel MD, from the University of Virginia, showed that collisions for males with ADHD steadily increased as they aged, contrary to the trend in the general population, or even women with ADHD. Therefore, adults with ADHD also seem more at risk, not just teens and young adults.

In the UK, ADHD has to be declared to the driving authority when you apply for a driving license. You can get the license, but it is punishable not to disclose the condition.

In conclusion, ADHD affects driving performance in adults of ages. This is undoubtedly due to the core features of ADHD: Inattention, hyperactivity/impulsivity, as well as emotional dysregulation. The comorbidity of specifically substance abuse, increases the risk. The risk of morbidity and mortality is high, and the economic cost is probably much higher than we could begin to calculate, in direct and indirect costs.

It becomes even more important to increase awareness of the condition and the risks associated with driving, increase accurate diagnosis, and then use education and driver trainer programmes, as well as medication, to lessen the risk. In adults, it is important, in my opinion, that adults use their medication consistently. This would include weekends and holidays, and especially when driving in traffic or long distances.

The topic needs more research and specifically in local conditions.

References
2. W.H.O. Epidemiological Study
3. Wonder et al. NY Acad Sci, 2001
7. Davidson MA, J of Att Dis, 2008
Cognitive Dysfunction in Attention Deficit Hyperactivity Disorder

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Akeso Clinic, Randburg

The DSM-5 defines six key domains of cognitive function. These domains include: language, learning and memory, social cognition, complex attention and executive function. Cognitive function in psychiatric and neurological disorders may be impaired and it is usual for multiple domains to be affected. It is important to define the nature and where possible the cause of cognitive deficits in these disorders as they too can severely compromise social and occupational integration, psychological development, mental health as well as quality of life.

These cognitive deficits or symptoms may range from a defining symptom of the disorder such as in Alzheimer’s disease to one of several core symptoms such as schizophrenia, to a non-core symptom but common comorbid symptom in depression. There is debate in the literature as to whether the cognitive deficits (attention, executive function) present in attention deficit hyperactivity disorder (ADHD) should be seen as a defining, core or non-core symptom of ADHD. Recent research by Silverstein et al. may clarify this as their study has demonstrated a strong correlation with the core ADHD behaviour symptoms (inattention and/or impulsiveness and hyperactivity) and executive function deficit and that core ADHD behaviour symptoms were strongly predictive of executive function deficit. There is evidence that executive function deficit may be a defining symptom of ADHD and that the behaviour symptoms of ADHD actually represent the subdomains of executive function. A criticism of the DSM-5 is that this relationship as well as the executive function subdomain of emotional control which could be recognised as one of the core symptoms of ADHD is not reflected in the diagnostic manual.

Executive function deficit is not unique to ADHD. This cognitive domain deficit is also seen in other psychiatric and neurological disorders. The understanding of the definition, neuroanatomical basis and presentation of executive functioning is paramount to the holistic assessment and management of such complex disorders.

Definition of Executive Function

The term executive function is used as an umbrella for various complex cognitive processes.

Executive function provides the mental skills that enable a person to successfully engage in goal-directed, independent, autonomous, efficient and socially adapted behaviours.

Executive function can be divided into subdomains and these include: sustained attention, planning, decision making, problem solving, reasoning, working memory, responding to feedback, inhibition of dominant or automatic responses when necessary, temporal processing (motor timing, time estimation) and cognitive flexibility. Inhibition results in the control over attention, thoughts, behaviour and emotions (see Figure 1).

The three core executive functions include working memory, inhibitory control and cognitive flexibility and the higher level executive functions include problem solving, reasoning, planning and monitoring. (see Figure 2) These functions can further be divided into hot executive functions (emotional regulation/processing, motivation control and reward-related decision making (temporal discounting)) and the cool executive functions involving complex cognitive processes (sustained attention, core and higher level functions).

Neuroanatomy of Executive Function

Since the advent of MRI and functional MRI researchers have been able to locate the areas in the brain associated with executive function deficit.

Executive functions involve primarily the prefrontal cortex. The cool executive functions are linked to the dorsal and lateral parts of the prefrontal cortex and the hot executive functions are linked to the ventral and medial parts of the prefrontal cortex.

- **dorsolateral prefrontal cortex** through extensive projections to posterior cortical regions (top down regulation)
- **ventrolateral prefrontal cortex** (inferior frontal cortex) through projections to the basal ganglia
- **ventromedial prefrontal cortex and orbitofrontal cortex** through extensive projections to subcortical areas such as the amygdala, nucleus accumbens, and brainstem.

- **Working Memory**: Temporary storage and active control
- **Inhibitory Control**: Ability to exclude irrelevant answers
- **Cognitive Flexibility**: Behaviour modification to different contexts

[Figure 1: Executive function domains.](#)

[Figure 2: Core and higher level function.](#)
Other brain areas involved
- Anterior cingulate cortex (cool and hot executive function)\textsuperscript{12,13}
- Ventral Striatum (hot executive function)\textsuperscript{12,13}
- Cerebellum - (cool executive function) co-ordination of behaviour, timing of behaviour and thought and anticipation of reward\textsuperscript{12,13}
- Thalamus - (cool executive function) modulates attention and filters interfering stimuli\textsuperscript{13}

(See Figure 3 and Figure 4)

The cortical networks involved in executive function are:\textsuperscript{10,12,13}
- The frontal-striatal-thalamic circuit
- The frontal-cingulate-parietal circuit
- The frontal-cerebellar circuit
- The frontal-limbic circuit

Executive Function Disorders
Executive function deficit may be seen in psychiatric and neurological disorders that affect the prefrontal cortex and associated cortical areas, or involve subcortical regions such as the basal nuclei (striatum). A disruption of the complex networks/circuits may also result in executive function deficit.\textsuperscript{8} Executive function disorders include:  

Neurological
- Head trauma
- Stroke
- Alzheimer’s disease
- Vascular dementia
- Frontal dementia
- AIDS dementia complex
- Huntington’s disease
- Foetal alcohol syndrome, prematurity
- Multiple systems atrophy
- Progressive supranuclear palsy
- Parkinson’s disease

Psychiatric
- Major depression
- Bipolar disorder
- Schizophrenia
- Autism spectrum disorder
- Learning disorder
- Obsessive compulsive disorder
- Conduct disorder
- ADHD

The three major executive function domains typically problematic in the above disorders include the following: working memory, inhibitory control/response inhibition and cognitive flexibility.\textsuperscript{7,10} There is, however, heterogeneity in the presentation of these dis-
Focus on ADHD and Executive Function Deficit

ADHD is recognised as a neurodevelopmental disorder in the DSM-5. ADHD is prevalent in 5% of children and 2.5% of adults. It is estimated that around 67% of children continue to exhibit symptoms into adulthood. Adolescents and adults with ADHD continue to experience inattention and impulsivity, however hyperactivity becomes less noticeable. Older adolescents and especially adults experience more serious and diverse cognitive deficits resulting in a higher risk of school and university failure, emotional problems, work and relationship problems and substance abuse problems.

Studies have shown that individuals with ADHD exhibit poorer performance on cognitive batteries than controls. These individuals demonstrate relatively consistent deficits in specific cognitive functions. These areas include complex attention and executive function. Individuals with ADHD as a result of executive function deficit consistently experience problems with emotional recognition, expression and regulation. They often present with irritability, anger, rage, aggression and mood swings.

ADHD cognitive batteries test the following functional domains:

Complex Attention
- Selective attention: the preferential processing of one stimulus in the presence of other stimuli (distractors)
- Sustained attention: the ability to continuously perform a task over a prolonged period without significant loss in performance
- Response precision: temporal or special precision in behavioral response to stimuli or relevant events

Executive Function
- Cognitive flexibility: the ability to switch between tasks without loss of performance, the ability to multitask
- Working memory: the ability to preserve a representation and active control of information over time, avoiding distraction
- Temporal information processing: the ability to accurately recognise or reproduce time intervals, time management
- Response inhibition: the suppression of actions, thoughts, and emotion that is inappropriate for a given task
- Planning and organising
- Task initiation
- Self-monitoring and regulation

Many studies have supported the link between ADHD and executive function deficit. Brain imaging research also supports this link. As mentioned earlier in the introduction, Silverstein et al confirmed that the DSM-5 defined core ADHD symptoms (inattention, hyperactivity and impulsivity) are correlated with and precipitated by executive function deficit. Unfortunately the current DSM-5 criteria does not link the core ADHD diagnostic criteria to the underlying cognitive domains implicated in ADHD or include emotional instability as a core symptom. Table 1 illustrates}

<table>
<thead>
<tr>
<th>Table 1: Clinical examples of executive function deficit</th>
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<tbody>
<tr>
<td><strong>EF component</strong></td>
<td><strong>Associated EFD Area of Weakness</strong></td>
</tr>
<tr>
<td>Response inhibition</td>
<td>Difficulty inhibiting responses; may blurt out answers; may seem to act without thinking.</td>
</tr>
<tr>
<td>Cognitive Flexibility</td>
<td>Perseveration on thoughts, concepts or tasks; difficulty shifting tasks, difficulty multitasking.</td>
</tr>
<tr>
<td>Setting and achieving goals</td>
<td>Difficulty setting appropriate goals and maintaining course; difficulty generating individual strategies for problem solving.</td>
</tr>
<tr>
<td>Task initiation</td>
<td>Reduction in self-generated behaviours; procrastination.</td>
</tr>
<tr>
<td>Planning, organisation and time management</td>
<td>Poor planning/organisational skills, inefficient use of time.</td>
</tr>
<tr>
<td>Abstract reasoning/concept formation</td>
<td>Use of concrete thinking; difficulty understanding consequences and cause-effect relationships.</td>
</tr>
<tr>
<td>Working memory</td>
<td>Difficulties accessing knowledge; forgetfulness.</td>
</tr>
<tr>
<td>Attention Control</td>
<td>Poor attention, distractibility.</td>
</tr>
<tr>
<td>Controlling emotions and social behaviours</td>
<td>Emotional lability; poor frustration tolerance; a tendency to blame others.</td>
</tr>
<tr>
<td>Self-monitoring and regulation/metacognition</td>
<td>Poor self-control; reduced insight; difficulty learning from past experiences.</td>
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<tr>
<th>Table 2: Executive function component and associated DSM-5 diagnostic criteria (designed by self)</th>
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<tr>
<td><strong>EF Component</strong></td>
<td><strong>Associated DSM-5 Diagnostic Criteria</strong></td>
</tr>
<tr>
<td>Cognitive Flexibility*</td>
<td>Does not follow through on instructions, fails to finish a task. Makes careless mistakes. Forgetful and easily distracted.</td>
</tr>
<tr>
<td>Task Initiation</td>
<td>Dislikes tasks that require mental effort over a long period of time.</td>
</tr>
<tr>
<td>Planning/Organising/Time Management</td>
<td>Loses objects necessary for tasks and activities. Has trouble organising tasks and activities. Fails to finish a task.</td>
</tr>
<tr>
<td>Working Memory*</td>
<td>Has trouble organising tasks and activities. Struggles to follow through on instructions, fails to finish a task. Forgetful.</td>
</tr>
<tr>
<td>Attentional Control</td>
<td>Seems not to listen when spoken to directly. Easily distracted. Trouble holding attention on tasks. Fails to give attention to detail, makes careless mistakes. Forgetful in daily activities.</td>
</tr>
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*Refers to core domains of executive function.
general examples of executive function deficit and Table 2 illustrates the link of executive function with the DSM-5 diagnostic criteria for ADHD.

The understanding of this link is very relevant clinically as ADHD severity increases the risk of having executive function deficit.4 It is important to screen all patients with ADHD for executive function deficit, to facilitate a comprehensive assessment and treatment programme as well as monitor response and improvement in functioning over time.4

Assessment and Diagnosis of Executive Function Deficit

Consider the following:2,3

• Take a detailed history from the patient and obtain collateral information from the family. Ask about executive function and give practical examples to illustrate.
• Conduct a physical examination and order blood tests, lumbar puncture, EEG and CT/MRI brain scan when indicated.
• Complete rating scales used to assess executive function, e.g. Behavioural Rating Inventory of Executive Function (BRIEF).
• Request a neuropsychiatric evaluation to evaluate the cognitive domains of executive function.

Treatment of Executive Function Deficit

Consider the following:17,18

• Use medication if there is a clear indication such as an antidepressant for depression, mood stabilisers and second generation antipsychotics for impulsivity, aggression and irritability. Use stimulants or nonstimulants to treat ADHD.
• If a medical cause is found, follow relevant treatment protocols.
• Behavioural and environmental changes:
  - Healthy diet and sleep patterns. Exercise regularly.
  - Try avoiding open plan working environments. Use earphones to block out the noise.
  - Take regular breaks.
  - Break down a task into smaller achievable goals. A time limit for completion must be set.
  - Use of rewards and incentives.
  - Regular review of performance, as this will ensure accountability and feedback.
  - Plan the day, prioritise tasks, and keep a routine.
  - Make use of calendars, diaries, post-it notes, alarm clocks, note pad, white board and apps on cell phone to help with planning, organising, prioritising, and time-management.
• Attend mindfulness and yoga training to help improve anxiety, attention and slow down impulsivity.
• Cognitive behavioural individual or group therapy that focuses on teaching new skills and compensatory behaviours, as well as challenging negative thoughts that prevent learning and change and can lead to depression and learnt helplessness.
• Dialectical behavioural group therapy will help with distress tolerance, emotional regulation and impulse control. There is also focus on inter-personal skills, assertiveness and anger management.

Conclusion

Executive function is one of the key cognitive domains defined by the DSM-5 and involves a complex set of processes that are essential for the achievement of goal orientated behaviours.7,16 Executive function deficits are not unique to neurological disorders but can also present in psychiatric disorders such as depression, schizophrenia, autism spectrum disorders and ADHD.8 Literature reviews describe a strong association with ADHD and executive function deficit and ADHD core behaviour symptoms are a strong predictive marker for executive function deficit.4 Thus all patients with ADHD must be screened for executive function deficit.4 ADHD medication will improve symptoms and performance in some cognitive areas such as attention however non pharmacological interventions such as behavioural and environmental interventions are essential when treating executive function deficit in ADHD.16

Points to Remember

• The DSM-5 defines six key domains of cognitive function which include: language, learning and memory, social cognition, complex attention and executive function.
• Executive function provides the mental skills that enable a person to successfully engage in goal-directed, independent, autonomous, efficient and socially adapted behaviours.
• The three core executive functions include working memory, inhibitory control and cognitive flexibility and the higher level executive functions include problem solving, reasoning and planning.
• Executive functions involve primarily the prefrontal cortex with projections to other parts of the brain including the parietal lobe, striatum, limbic system and cerebellum.
• Executive function deficit can occur in psychiatric and neurological disorders and presents as a defining symptom or one of the core symptoms or a comorbid symptom of the disorder.
• There is a strong correlation with the core ADHD behaviour symptoms (inattention and/or impulsiveness and hyperactivity) and executive function deficit.
• The core ADHD behaviour symptoms are strongly predictive of executive function deficit and there is evidence that executive function deficit may be a defining symptom of ADHD.
• Pharmacological as well as behavioural and environmental interventions are necessary to treat executive function deficit in ADHD.

References for Cognitive Dysfunction and ADHD
3. De Bustamante D; Fichman C. Neuropsychological Assessment of ADHD and Executive Function Deficits in Adults. ADHD in Adults 2012:59-70.
Attention deficit hyperactivity disorder (ADHD) is the most common neuro-developmental disorder in children. The prevalence of ADHD is reported from 1.0% to 7% in school-aged children all over the world and is three times more likely to occur in boys compared to girls. ADHD is characterised by a combination of symptoms of inattention, impulsivity and hyperactivity that interfere in functioning, social development or both and the symptoms usually persists into adulthood. ADHD is a genetic complex and highly heritable brain disorder but it is still unclear how specific genes interact with adverse environmental factors to produce various brain abnormalities observed in ADHD.

Worldwide 7-15% of children are affected by asthma, making it the leading cause of chronic childhood disease. The global prevalence of other allergic diseases, atopic dermatitis (AD), allergic conjunctivitis (AC) and allergic rhinitis (AR) is also increasing.

The association between ADHD and allergic diseases, whether rooted in comorbidity or causality, has been a source of public and clinical interest since the 1980’s. Some studies have suggested that the relationship between the immune response and the central nervous system (CNS) may predispose some children to autism, impulsive behaviour and ADHD. Several epidemiologic studies have reported that children with ADHD have a high risk of developing allergic diseases, while other studies have reported no evidence of a link between allergy and ADHD.

Allergic sensitisation is an important risk factor for the development and severity of allergic diseases. Both ADHD and allergic sensitisation depend on a complex interaction between genetic and environmental factors. If allergic sensitisation is associated with ADHD, prevention of allergic sensitisation might play a role in decreasing the burden of ADHD.

They found AD with allergic sensitisation to be associated with ADHD. The hallmark pathology of AD is immunological irregularities such as high immunoglobulin-E (IgE), increased eosinophilic activity and a predominantly T helper type 2 cytokine secretion. They found AD with allergic sensitisation to be associated with ADHD. They did not find a positive relationship between food allergens and ADHD in this study.

Their study interestingly showed that mite sensitisation was significantly associated with ADHD.

Their conclusion is that just as allergic sensitisation is essential for allergic disease, allergic sensitisation is also assumed to play a critical role in ADHD.

Yang et al
In a large-scale, population-based study Yang et al looked at the association between allergic diseases, allergic sensitisation and ADHD in children in Taiwan. They conducted a cross-sectional survey on 2772 children to investigate the relationship between allergic diseases, allergic sensitisation as measured by skin prick tests and ADHD.

They found AD with allergic sensitisation to be associated with ADHD. The hallmark pathology of AD is immunological irregularities such as high immunoglobulin-E (IgE), increased eosinophilic activity and a predominantly T helper type 2 cytokine secretion. A growing number of studies suggest that inflammatory cytokines released during the atopic response may pass the blood-brain barrier and activate neuro-immune mechanisms (such as stress) that have emotional and behavioural relevance. AD is associated with high levels of psychosocial stress that may lead to dysfunctional mother-child relationships, sleep disturbances, less physical contact and later stigmatisation and bullying by peer groups. Their study indicates that increased stress exposure can effect multiple neurotransmitter and neuroendocrine systems, which leads to long-term alterations in the behavioural and physiological repertoire, thereby increasing vulnerability to psychopathological conditions such as ADHD.

Their study also showed asthma with allergic sensitisation to be a risk factor for ADHD, but AD and asthma without allergic sensitisation were not. The mechanism underlying the development of ADHD in children with asthma is unclear. It can be that patients with AD and asthma with allergic sensitisation are more sensitive to disturbing factors due to higher levels of cytokines, IgE, or higher levels of psychological stress, and so have a higher significant association with ADHD.

Melamed et al
Melamed et al investigated the relationship between ADHD and allergic rhinitis (AR).
AR affects up to 30% of all children. It has been suggested that neurotrophic protein nerve growth factor (NGF) might serve as a vehicle for cross talk between the immune and nervous systems. NGF:

- regulates immunoglobulin production (particularly IgE regulation), and
- plays a major role in the control of allergic inflammatory response, serving as one of the critical proteins in the cross talk between the immune and nervous systems and the endocrine system.

In this study they looked at the synergistic effects of treatment with both antihistamines and stimulants and to determine the role of NGF in ADHD and AR.

For seasonal allergic-related symptoms, a two-drug combination of methylphenidate and cetirizine proved to be superior to either drugs alone in reducing Total Symptom Severity Complex scores and ADHD symptoms. The study supports the hypothesis that, in children diagnosed with ADHD, there is a subset of children who also suffer from atopic disease. They propose that a cascade of events initiated by various stimuli (i.e., environmental factors, food, stress, or infection, in a person who is genetically predisposed to atopy) may trigger an immune inflammatory cascade that may lead to neuro-immune inflammation presented clinically as ADHD. In this study, the role of NGF was demonstrated by the modulating effect of the antihistamines and stimulants on NGF levels in patients with comorbid disease. NGF suppression had a direct correlation to clinical improvement.

Miyazaki et al
Miyazaki et al did a systematic review and meta-analysis on allergic disease in children with ADHD. The comprehensive search identified a total of 261 studies from the databases of which only 5 observational studies met the inclusion criteria. There were no eligible RCT studies identified related to ADHD and allergies. There was a total of 61,811 children involved in the 5 studies and 62% were male. Of the 61,811 children 13% were diagnosed with ADHD. The results are as follow:

**Asthma**
The meta-analysis showed that children with ADHD were nearly twice as likely to have asthma compared with those in control groups with an 80% increased odds.

The high asthma rate in children with ADHD could potentially be linked to a recent discovery of a genetic association, in which several studies suggested that a gene polymorphism of dopamine receptor 5 (DRD5), a form of dopamine D1-like receptor, is associated with a ADHD behaviour subtype and that the expression of DRD5 is found in both the mammalian brain and peripheral blood leucocytes. According to these reports, DRD5 may also engage in some part of the immunological regulation process of T helper 17 cell differentiation, which is extensively involved in asthma development.

**Allergic rhinitis**
The result from the combined studies showed that a higher proportion of children in the ADHD groups had AR compared to control groups. This suggests that children with ADHD experienced 59% greater odds of having AR relative to the children without ADHD. There were however substantial evidence of heterogeneity and inconsistency detected among the studies.

**Atopic dermatitis**
From the pooled estimate across the studies, the relative effect indicated a significant difference between the ADHD and control groups, but again with considerable heterogeneity and inconsistency across the studies. ADHD groups had higher odds of AD than the control groups, but in some studies only slightly higher.

**Allergic conjunctivitis**
The pooled estimate showed a higher proportion of children in the ADHD group experienced AC compared with the control groups.

**Food allergy**
The meta-analysis showed no difference between the ADHD groups and control groups. One underlying reason for this could be the complexity of the IgE immune response to food allergens in the gastro-intestinal tract falling between the tolerance and sensitising mechanisms.

**Other concerns**

**Growth patterns and medication.**
Monitoring physical growth in children is an integral part of paediatric practice. Growth perturbations from stimulant medications and inhaled corticosteroids (ICS) have been an area of concern. Stimulant medication for the treatment of
ADHD and ICS for the treatment of asthma are two classes of medications that are commonly prescribed in paediatrics. Among other adverse effects of these medications, growth attenuation has long been a focus of investigation. With stimulants, growth deficits of 1-1.4 cm/year have been observed in the short term, mainly in the first two years of treatment, in a dose-dependent manner. Long-term studies have reported divergent effects on growth, with many studies showing no clinically significant height deficits by adulthood. The study that followed the largest cohort of children on stimulants (MTA) however reported an overall height deficit of 1.29 cm in subjects who have received stimulant medications, with mean height deficit of 4.7 cm in those taking the medicine consistently. With ICS use, mild growth suppression is seen in the short term (particularly the first year of treatment) with growth rates reduced by 0.4-1.5 cm/year. Available current evidence indicates that the impact of ICS on adult height is not clinically significant, with the effects limited to 1.2 cm or less.

Based on currently available evidence, the therapeutic benefits of ICS for management of asthma and stimulant medications for management of ADHD outweigh the potential risk of growth suppression. Strategies to minimise growth attenuation and other potential adverse effects of these medication include using the lowest efficacious dose, frequent assessments and dose titration. Particular vigilance is essential with concomitant use of multiple medications.

Poverty, ADHD and allergies

Poverty negatively affects the development and well-being of children and adolescents in a variety of ways. Poor children are often exposed to inadequate nutrition, violence and environmental toxins among others. Children in poverty with chronic conditions are also more likely to have higher rates of comorbid disorders and worse outcomes. The National Survey of Children’s Health (2011-2012) was associated with a higher parent-reported prevalence of asthma and ADHD.

A study by Pulcini et al suggests that the national rise in parent-reported prevalence of asthma, ADHD and autistic spectrum disorder (ASD) as well as comorbid disorders is differentially influenced by poverty status, such that being poor was predictive of a higher prevalence for asthma and ADHD but not for ASD. Poor children with asthma and ADHD was associated with more comorbidity.

In view of this article and the issues discussed, the influence of poverty in the South African situation must not be underestimated.

Some medications currently used to treat allergic disease may adversely affect the CNS and contribute to learning impairment, poor school performance and attendance.

Conclusion

Reports of frequent manifestation of allergic diseases in children with ADHD have been the subject of mounting clinical interest. Recent findings from population-based and review and meta-analysis show that children with ADHD are more likely to have asthma, AD, AR and AC than their counterparts. The underlying neuro-biological and immunological mechanisms needs to be investigated further.

References

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