Attention Deficit Hyperactivity Disorder – an overview

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ABSTRACT
Attention Deficit Hyperactivity Disorder (ADHD) is a neurobehavioural disorder found more commonly, but not exclusively, in school-age children. The hallmarks of the condition are inattention and hyperactivity/impulsivity, which often go together. Although the term ADHD was coined relatively recently, ADHD has in fact been described as early as 1902. This review article will go through the most important historical aspects of the condition, and will also give an account of what is known about the aetiology of ADHD. The diagnostic criteria issued by the American Psychiatric Association in DSM-5, have been last updated in May 2013. This article will highlight the differences between DSM-5 and the previous version, DSM-IV-TR, and will also touch upon the latest developments in electroencephalography-based investigations and imaging studies for ADHD. Although the condition cannot be cured, symptoms can be managed using various modalities such as behaviour intervention strategies and medication, such that the individual affected by ADHD can have the least possible disruption to social and academic functioning.

HISTORY
The recognition of ADHD as a neurobehavioural disorder goes back over one hundred years, although the term ADHD was only coined in 1987. In 1902, Sir George Frederick Still (1868-1941) published a paper in The Lancet entitled, ‘Some abnormal psychical conditions in children: the Goulstonian lectures’. He described 43 children who he had come across in his practice, who displayed behavioural features that could today be attributed to ADHD, such as poor attention, difficulty with self-regulation, emotional lability, disinhibited behaviour and normal cognitive functioning. Still chose to call this constellation of features, ‘Disorders of Moral Control’.

In 1917, the Romanian psychiatrist and neurologist, Constantin von Economo (1876-1931) described the encephalitis epidemic that was rampant between 1915 and 1926 mainly in Europe and North America. This atypical form of encephalitis was known as encephalitis lethargica or Von Economo disease. Adult survivors often developed a parkinsonian-like post-encephalitic phase, sometimes after a latent period of several years, while children tended to develop behavioural difficulties, including overactivity, impulsivity and poor coordination (Arnold, 1995; Wender, 1995). This was called minimal brain dysfunction-like behaviour. Von Economo also described the histology and showed that encephalitis lethargica mainly affected the dopamine-rich areas of the brain, often with autoantibodies against human basal ganglia antigens. Nowadays, it is widely known and accepted that the dopamine pathway is affected in ADHD sufferers (Dawei et al., 2006).

In 1923, Franklin G. Ebaugh, an American physician, published a paper in the American Journal of Diseases of Children entitled ‘Neuropsychiatric sequelae of acute epidemic encephalitis in children’. Ebaugh was the
first to realise that ADHD could be the result of brain injury in children who had no prior behavioural issues (Spencer, 2007).

In 1937, Charles Bradley (1902-1979), a Rhode Island paediatrician, made an unexpected discovery when he realised that children who had behavioural difficulties and poor academic performance, showed a marked improvement when given benzedrine, a stimulant. At the time, Bradley was carrying out diagnostic procedures called pneumoencephalographies, where most of the patient’s cerebrospinal fluid (CSF) was drained to be replaced by air or helium, thereby obtaining a clearer X-ray image of the brain. Benzedrine was administered so as to increase CSF production and reduce the severe headaches that were so common after this procedure. In 1936, benzedrine was FDA-approved as treatment for ADHD symptoms (CDC, 2014).

**EPIDEMOLOGY AND AETIOLOGY**

The American Psychiatric Association reports that 5% of children have ADHD (APA, DSM-5, 2013). However, the CDC data obtained from the National Survey of Children’s Health which has been carried out every 4 years from 2003, quotes a much higher figure of around 11% of children aged 4-17 years. The diagnosis is on the increase, 5% per year increase over the period 2003–2011. It is more common in boys (13.2% in boys, 5.6% in girls), with an average age at diagnosis of 7 years (CDC, 2013). Approximately half of all children with ADHD go on to have symptoms in adulthood. The National Resource Centre on AD/HD (2014), quotes a prevalence rate of ADHD in adults in the United States, of 4.4%.

It is widely accepted that ADHD is a neurobiologic disorder primarily affecting the dopamine and noradrenaline pathways in the brain (Medscape Pediatrics, n.d.), with a strong genetic influence (Ross, 2012). There is a 50% concordance in first degree relatives. Several other factors have been attributed to the aetiology of ADHD, especially antenatal complications, prematurity and low birth weight, as well as tobacco smoking and alcohol consumption by the mother during pregnancy. Postnatal injury to the prefrontal areas of the brain has also been implicated (CDC, 2014). It is thought that azo dyes, a type of synthetic food colouring, may have an impact on ADHD behaviours, probably by causing zinc deficiency and, thereby, interfering with the processes that eliminate mercury from the body (Dufault, 2009). To this effect, in July 2008, the European Union ruled that as of July 2010, apart from the relevant E number for the particular azo dye, the product must clearly display the phrase ‘may have an adverse effect on activity and attention in children’ (McBurney, 2011). Studies show no cause-effect relationship between sucrose ingestion and ADHD (Benton, 2008). However, an important point of consideration is that the sugar that is found ubiquitously in processed foods, particularly sweets and sugary drinks, is not sucrose but high fructose corn syrup (HFCS), and therefore, one can only conclude that a high-sucrose diet, not a high-sugar diet, does not cause ADHD. HFCS is often contaminated with mercury while it is produced, and further studies are needed to determine whether ingestion of HFCS is associated with ADHD (Dufault, 2009).

Exposure to heavy metals from the diet, particularly in the prenatal period and in the first few years of life, has an impact on ADHD. High body lead levels have long been known to cause neurobehavioral problems. Mercury exists in two main forms – the inorganic form that is found mainly in soil and water, and the organomercurials. The earliest evidence that mercury is toxic to humans dates from the 1950s-1960s when mercury-containing industrial effluent from acetaldehyde production, was discharged into Minimata Bay, Japan. The result was that people who consumed fish and seafood caught from the bay in question, developed neurological and developmental disorders. Methylmercury is an organic type of mercury that is concentrated in the aquatic food chain. Current FDA recommendations for pregnant women are to eat no more than two portions (12 ounces or 340g) of fish or seafood per week, and to choose fish that is relatively low in mercury, such as salmon, shrimp, pollock, canned light tuna and catfish. Due to their high mercury levels, shark, swordfish, king mackerel and tilefish should be avoided in pregnancy, so as to reduce exposure of the foetus to the heavy metal (FDA, 2004).

Ethylmercury is another type of organic mercury, which however, appears to be less toxic to humans because it is metabolized and excreted differently to methylmercury. The main way in which humans are exposed to ethylmercury is through thiomersal, a preservative used first in the 1930s in biological products and some vaccines, but is now being phased out (FDA, 2014). Thiomersal is still used in some multi-dose vials of inactivated influenza vaccine, but these are not imported in Malta and Gozo. As a result, all vaccines that are administered to children and pregnant women locally, are thiomersal-free or have a trace amount of thiomersal (<1 microgram of mercury per dose).
An interesting study that looked at the effects of mercury (from seafood) and lead (from gunshot pellets in birds and animals that are hunted for food) in Arctic Canada, showed that prenatal methylmercury exposure was linked to ADHD symptoms later in childhood, and that even a low lead level in childhood, is associated with ADHD (Boucher et al., 2012).

**DIAGNOSIS**

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), was issued by the American Psychiatric Association on 18th May 2013 (APA, DSM-5, 2013). This replaced the previous DSM-IV-TR version. Table 1 highlights the changes in DSM-5 as compared to the previous edition. DSM uses the term ADHD, which is then subclassified into three presentations. The World Health Organization’s (WHO) International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10), in use since 1992, uses the term Hyperkinetic Disorder (HKD), with ADHD listed as a subcategory. ICD-10 will be superseded by ICD-11 in 2017. The DSM-5 criteria cater for adolescents and adults who have ADHD symptoms, which were not necessarily present in early childhood.

The diagnosis of ADHD is made by obtaining a detailed history from the parents, caregivers and teachers, and from the adolescent or adult patient. Behaviour rating scales, of which there are several available, are the main tools used to diagnose ADHD. Conners Rating scale, perhaps the most well known and widely used system, was devised by Carmen Keith Conners, a clinical psychologist who set up the ADHD program at Duke University, USA. This behaviour rating scale is currently in its third edition, Conners 3TM, to reflect

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<tr>
<td>ADHD listed under Disruptive Behavior Disorders</td>
<td>ADHD listed under Neurodevelopmental Disorders</td>
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<tr>
<td>9 inattentive &amp; 9 hyperactive-impulsive behaviours listed</td>
<td>examples given of behaviours expected in older child/adolescent</td>
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<td>6 symptoms needed to make a diagnosis</td>
<td>only 5 symptoms needed to make a diagnosis in &gt;17 years &amp; adults</td>
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<td>symptoms which are not in-keeping with child’s developmental level, present for 6 months or longer</td>
<td>symptoms must be present, but not necessarily cause impairment, by 12 years of age</td>
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<td>symptoms must be present and cause impairment by 7 years of age</td>
<td>several symptoms present in two or more settings</td>
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<td>symptoms cause some impairment in at least 2 settings</td>
<td>‘clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning’</td>
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<td>‘clinically significant impairment in social, academic or occupational functioning’</td>
<td>3 presentations: Predominantly Inattentive Presentation, Predominantly Hyperactive-Impulsive Presentation, Combined Presentation</td>
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<td>3 subtypes: Predominantly Inattentive Type, Predominantly Hyperactive-Impulsive Type, Combined Type</td>
<td>Can change from one to the other</td>
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<td>If symptoms no longer fulfill diagnostic criteria, specify in ‘Partial Remission’</td>
<td>ADHD diagnosis made as mild, moderate or severe</td>
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<td>ADHD cannot be diagnosed with Autistic Spectrum Disorder</td>
<td>Recognizes that ADHD can coexist with Autistic Spectrum Disorder</td>
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the new DSM-5 criteria (Conners, 2013). Perhaps the major flaw of such a behaviour rating scale, which is in the form of a questionnaire that requires the person to rate the particular behaviour on a score from 1-5, is its subjectivity. A physical examination, including a vision and hearing test should be done to exclude other conditions. Body lead levels are only indicated if the history is suggestive of a high lead exposure.

Imaging studies, including single-photon emission computed tomography (SPECT), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI), have shown that there is about a 3 year delay in brain maturation and some differences in brain activity in children with ADHD when compared to controls (Watson, 2013). SPECT, a costly procedure, which uses an injectable radioactive substance to measure blood flow and brain activity, is not yet FDA-approved for ADHD diagnosis. In July 2013, FDA approved the first brain imaging test for ADHD diagnosis in patients of 6-17 years of age. This Neuropsychiatric EEG-Based Assessment Aid (NEBA) System is a 15 minute EEG-based test which measures the theta-beta ratio of brain waves emitted (FDA, 2013). This ratio is known to be higher in individuals with ADHD as compared to controls. The procedure, pioneered by Howard Merry, has come under criticism because of the way FDA approved the test based only on Merry’s study of 275 individuals, and also because of the cost involved to carry out this test (Brauser, 2014). NEBA is not a stand-alone diagnostic test for ADHD, but should be used in conjunction with the standard behaviour rating scales and fulfilment of DSM-5 criteria. It remains to be seen whether NEBA is useful in distinguishing ADHD from bipolar disorder in adolescents, a distinction that can be very difficult to make accurately.

It is imperative that a diagnosis of ADHD is made accurately by stringent use of the DSM 5 criteria. Otherwise, we run the risk of overdiagnosing and overtreating patients. Some leading figures in the ADHD field have questioned whether ADHD really does exist. To cite one example, reference is made to an opinion piece that was published on Time on 14th March 2014 by Dr Richard Saul, a fellow with the American Academy of Paediatrics and an associate fellow of the American Academy of Neurology. ‘I’ve come to believe based on decades of treating patients that ADHD — as currently defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) and as understood in the public imagination — does not exist’ (Saul, 2014).

**MANAGEMENT**

Apart from the use of medications, the management of ADHD involves behavioural intervention strategies and educating the family on how to deal with the condition. It also has implications on schooling - some children with ADHD may benefit from the help of a Learning Support Assistant.

The Feingold® diet is an elimination diet that is free from dyes, artificial flavours, sweeteners and preservatives, and can be used both as a diagnostic tool to determine whether any dietary factors are negatively affecting ADHD behaviours, as well as a treatment modality for ADHD. Using a double-blind randomised controlled trial, Rucklidge et al., (2014), showed that a micronutrient supplement consisting of various vitamins and minerals may have some efficacy in managing adults with ADHD.

Drugs are FDA-approved from 6 years of age, and once started, it is recommended to stop the treatment for a couple of weeks, usually in the summer, so as to determine whether the patient still requires medication or not. Other factors to keep in mind are adverse drug effects, drug interactions, co-morbid conditions and parent and child-preferences.

The two main groups of drugs for ADHD treatment are the stimulants and non-stimulants. The drugs that are available locally are the stimulants Ritalin® and Concerta® (both methylphenidate) and the non-stimulant Strattera® (atomoxetine).

Methylphenidate is a dopamine-reuptake inhibitor, and so increases extracellular dopamine in the striatum. Ritalin® is an immediate-release form with a duration of action of 3-4 hours (SPC Ritalin®, 2013), whereas Concerta®, which is intermediate-release with a duration of action of up to 12 hours (SPC Concerta®, 2014), has the advantage of once daily dosing. The dose is increased in a stepwise fashion over a 4 week period. Around 75% of patients respond to treatment, while the remainder either show no improvement or have side effects which necessitate stopping the drug. The most common side effects are reduced appetite, transient weight loss, irritability and sleep disturbance. In January 2009, the European Medicines Agency (EMEA) issued some recommendations on the safe use of methylphenidate (EMEA, 2009). Because of the cardiovascular and cerebrovascular risks, all patients should have their blood pressure and heart rate measured before starting treatment, and every 3 months while on medication. Prior to starting methylphenidate, one should ask about...
a family history of cardiovascular disorders, and in those patients with a positive family or personal history or an abnormal cardiovascular examination, an ECG and cardiology consultation would be warranted. The patient’s height and weight should be measured, and one must look out for the development of psychiatric disorders.

The use of methylphenidate locally has shown a 4 fold increase since the year 2000, as shown in Figure 1. Strattera® is a selective noradrenaline reuptake inhibitor, with a duration of action of 12 hours. It is usually given as a single daily dose in the morning, and the capsule has to be swallowed whole. The most common side effects are sleep disturbances, fatigue, nervousness, dry mouth and stomach upset. Suicidal ideation (0.4% in Strattera-treated group as compared to 0% in the placebo group); severe liver injury, including hepatic failure, which was only picked up in post-marketing surveillance of the drug; and sudden deaths in children who had an underlying structural cardiac abnormality, have been reported (SPC Strattera, 2013).

**ASSOCIATED IMPAIRMENTS**

People who suffer from ADHD, may also have associated impairments. The most common problems are difficulty in peer-relationships and an increased risk of injuries. An associated learning disorder is found in approximately half of 6-11 year olds with ADHD. Data from the CDC National Health Interview Survey (2008) shows that in the US over the period 2004-2006, 5% of children aged 6-17 years had ADHD without a learning disability, 5% had a learning disability without ADHD, and 4% had both conditions. Oppositional Defiant Disorder and Conduct Disorder are less common.

The ADHD Family Support Group Malta is a non-governmental organization which holds monthly meetings for families of ADHD-sufferers as well as the public in general.

**CONCLUSION**

Over the past years, ADHD has been studied closely and much research has been carried out, particularly to elucidate the aetiology of the condition, to make a more accurate and timely diagnosis, and for effective treatments to be made available. However, much still remains to be known.
Reference


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