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REVIEW ARTICLE

The current status of research into attention deficit hyperactivity disorder: proceedings of the 2nd international congress on ADHD: from childhood to adult disease

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Abstract Despite being a devastating psychiatric condition with high prevalence, ADHD has traditionally been widely under-researched, specifically in adult patients. Therefore, the recent surge in scientific projects focusing on ADHD is impressive. By reviewing selected research findings presented at the 2nd International Congress on ADHD, this paper gives an overview about current state-of-the art research in such different areas as diagnosis, classification, epidemiology, differential diagnosis and comorbidity, neurobiology (including molecular genetics, proteomics, neuroimaging and electrophysiology), environmental factors, modelling of ADHD, treatment (pharmacological and non-pharmacological), as well as forensic and social aspects.

Keywords ADHD · Pharmacotherapy · Psychotherapy · Biological psychiatry · Genetics · Proteomics

Introduction

This year's conference covered a plethora of ADHD-related issues both in childhood and adolescence as well as in adulthood, a so-far under-researched area whose importance fortunately gains increasing recognition. Clinical issues including diagnosis, prognosis, treatment and prevention were addressed, as were research issues encompassing neurobiology, genetics, proteomics, imaging and model systems. At the same time, the important social and forensic implications of ADHD were not neglected, but intensely discussed based on the findings of the presented studies, both in symposia and oral sessions as well as in guided poster tours.

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Diagnosis, classification, epidemiology

Despite progress made in recent years regarding diagnosing ADHD in children/adolescents and in adults, modern international classification criteria such as DSM and ICD remain not fully satisfactory. There is clearly room for improvement and differences between such systems and other shortcomings will hopefully be addressed in forthcoming editions (Rohde 2009b; Steinhausen 2009). One of the main messages of this congress is the proposal of the DSM-V committee that a "Late Onset ADHD" will be introduced as a new category (Rohde 2009b).

Additionally, it remains important to develop new assessment tests for ADHD, since such psychometry can further improve attempts to clarify diagnoses. In this context, a new auditory continuous performance test was presented (Quinn and Elias 2009). Neuropsychological/executive dysfunction can often be observed in patients with ADHD; however, its assessment is not recommended in the routine clinical diagnostic assessment (Tannock 2009).

At the same time, there is increasing evidence that ADHD is a worldwide transcultural phenomenon and exhibits striking and consistent characteristics which seem to be independent of cultural background. While cultural differences remain important considerations when it comes to diagnosing, treating and researching ADHD, there are emerging data pointing to trans-cultural common features of ADHD. Given this background, the international and

worldwide contributions to this conference were important in order to avoid a "Western-centric" perspective. For example, an Iranian study reported a prevalence of more than 10% in boys and approximately 4% in girls (Alizadeh and Armion 2009). A Ukrainian study reported a prevalence of roughly 8% (Martsenkovska and Martsenkovsky 2009).

Regarding the pathogenesis of ADHD, Sonuga-Barke (2009) put forward the so-called default mode interference hypothesis. Detailed in a seminal paper (Sonuga-Barke and Castellanos 2007), this theory puts forward that variability in performance is based on "neural-activation failure" when switching from a resting state to activity (Sonuga-Barke 2009). Interestingly, it seems to be possible to elucidate biological factors which support this hypothesis, using electrophysiological and neuroimaging techniques. Brain areas involved are the prefrontal and parietal cortex, and motor areas. Additionally, this group has published several recent papers looking into the role of gene variants in modulating psychological phenomena and behavioural problems in ADHD (Sonuga-Barke et al. 2009).

Differential diagnosis and comorbidity

It is almost a common place statement that ADHD is often associated with one or more comorbid conditions. For example, ADHD might represent a risk factor for certain types of personality disorders which might have important implications for therapy and prevention programmes (Fossati and Borroni 2009), and ADHD seems to be more prevalent in patients with mental retardation (Ivanov et al. 2009). There also seems to be a link between ADHD and eating disorders and obesity in children (Herpertz-Dahlmann and Ravens-Sieberer 2009). A further challenging phenomenon in ADHD is mood swings. Affective dysregulation is an important issue in children with ADHD (Holtmann 2009), and in adult patients with ADHD, comorbidity with bipolar disorder must be carefully distinguished from frequently observed mood swings, an often difficult diagnostic challenge, with important therapeutic implications, since bipolar patients with ADHD can benefit from ADHD medication in addition to their mood stabilising pharmacotherapy (Fallu et al. 2009).

There is a broad overlap between ADHD and autism spectrum disorder (Dineen and Fitzgerald 2009; Roy et al. 2009; Sinzig et al. 2009). Other important comorbid conditions include anxiety (Edel et al. 2009; Dineen and Gallagher 2009), bipolar disorders (Bernardi et al. 2009; Halmoy et al. 2009) oppositional defiant and conduct disorder (Alvaani and Dalvand 2009; Franc et al. 2009) and substance use (Feuz and Tschacher 2009).

A clinically important, yet not sufficiently understood problem consists of the symptomatological changes occurring during ageing (Klein and Mannuzza 2009), not only regarding the symptoms of ADHD but also in respect to comorbid conditions. The comorbidity spectrum in childhood is different from that in adolescence and this in turn again different from that in adulthood. This finding represents one of the key messages of the congress: ADHD comorbidity varies with age and it is therefore appropriate to speak of "developmental comorbidity".

A further fascinating and rapidly evolving research area is ADHD and circadian rhythmicity which may have important clinical implications. For example, adult patients with ADHD show more risk factors for general physical health problems that may be related to disturbances of biological rhythms (Boonstra et al. 2009).

In this context, Kooij and co-workers focused on the emerging field of the role of circadian rhythms in ADHD (Kooij et al. 2009). Based on the observation that many adult patients with ADHD suffer from a disturbed sleep pattern, Kooij and team further explored whether such patients prefer mornings or evenings regarding their daily activity patterns using standardised questionnaires and actigraphy via so-called actiwatches, little watch-like devices which are worn by study individuals over a prolonged period of time and which register activity and rest patterns. Obviously, adult ADHD is associated with "eveningness". About 80% of adult patients with ADHD exhibit a chronically delayed sleep pattern. Additionally, melatonin expression levels are significantly altered. These findings are of special relevance since circadian rhythmicity is determined both by environmental (light exposure, day/night rhythm) and genetic factors (CLOCK genes). First studies are underway to look into possible associations between ADHD and variants in CLOCK genes (Kissling et al. 2008). In an earlier study, this group had shown that adult patients with ADHD take longer to fall asleep, have lower sleep efficiency and have shorter periods of uninterrupted sleep (Boonstra et al. 2007). Interestingly, methylphenidate reduces total sleep time, but seems to improve "sleep quality by consolidating sleep" (Boonstra et al. 2007).

Neurobiology

Molecular genetics

Many genes contribute to the pathophysiology of ADHD and interact with each other. The molecular genetics of ADHD is complex, since—like in many other neuropsychiatric conditions—the potential neurobiological subtypes (nosological entities) do not necessarily differ in their clinical phenotype, i.e. phenomenological manifestation. Major progress has been made in elucidating the genetic

background of ADHD. Association and linkage studies, as well as whole genome scans will continue to further clarify which genes might increase the risk for this condition and which might have protective properties. Possibly, there is some association between ADHD and polymorphisms of genes involved in the dopaminergic neurotransmitter system such as DRD4, DRD5, DAT, COMT and MAOA. Recently identified possible candidate genes include CDH13, SLC9A9 and LPHN3 as well as ASTN2, DIRAS2, CTNNA2, KALRN, NOS1, GIRK2 and CNR1 (Asherson 2009; Franke 2009; Jacob et al. 2009; Leung et al. 2009; Renner et al. 2009; Qian et al. 2009; Weißflog et al. 2009). A variant of the latrophilin 3 gene (LPHN3), possibly together with other polymorphisms, could predict treatment outcome (Deckert 2009; Muenke 2009). Furthermore, genes involved in synaptic plasticity such as genes coding for synaptic vesicle proteins might be other promising genetic candidates (Chen et al. 2009). This research approach might also help to identify genetically distinct ADHD subtypes (Larsson 2009). Furthermore, while twin studies already suggested a certain overlap between ADHD and reading and writing disabilities, there are interesting molecular findings confirming such a "genetic overlap" between dyslexia and ADHD (Wigg et al. 2008). Additionally, there is exciting research focusing on gene–gene and gene–environment interactions, an emerging and promising field of future research.

Proteomics

While one of the main focuses of neurobiological research into ADHD remains the area of molecular genetics, it is increasingly recognised that genetic alterations alone cannot explain in full, complex pathophysiological processes. Therefore, proteomics has emerged as an important research area which aims at addressing this issue by shifting the focus of attention towards the protein level. Analysing potentially altered protein profiles might be useful in the identification of biomarkers of ADHD and other neuropsychiatric disorders (Hünnerkopf et al. 2009).

While proteomics aims at analysing the totality of human proteins and their complex interactions, traditional hypothesis-driven research projects focusing on specific molecules, remains an important approach. For example, it was suggested that catecholamine levels are altered in urine samples of patients with ADHD (Salavessa et al. 2009) and that they may also exhibit an altered cortisol response (van West et al. 2009).

Neuroimaging and electrophysiology

Structural and functional imaging reveals a plethora of subtle alterations in the brains of patients with ADHD. Additionally, functional imaging might be specifically useful in defining so-called endophenotypes which then can be linked to specific gene variants (Dunston 2009a, b). Furthermore, fMRI reveals abnormal functional connectivity in patients with ADHD (Li et al. 2009), and there seems to be a pattern of persistent fronto-striatal dysfunction (Cubillo et al. 2009a). A dysfunction in the inferior prefrontal cortex during inhibitory control, which can also be detected via fMRI, seems to be an ADHD-specific alteration which cannot be detected in other psychiatric conditions such as OCD or conduct disorder (Rubia et al. 2009).

Depending on the subtype, adults with ADHD exhibit, in fMRI, a reduced activation and inter-regional functional connectivity of fronto-striatal networks and/or fronto-cerebellar brain dysfunction (Cubillo et al. 2009b, c). Boys with ADHD exhibit abnormal baseline brain activity when assessed via resting-state functional MRI (An et al. 2009).

Altered amplitudes in event-related potentials (ERP) were found in several studies (Bakhtadze et al. 2009; Inoue et al. 2009a; Lenz et al. 2009; Yakovenko and Nikishena 2009). Furthermore, there are distinct changes in EEG recordings with quantitative source density analysis (Brechtel and Dimpfel 2009).

In line with the findings mentioned earlier, near-infrared spectroscopy (NIRS) revealed reduced prefrontal activation during response inhibition in children suffering from ADHD (Inoue et al. 2009b). Interestingly, there are also indications that adult patients with ADHD suffer from altered cortical olfactory processing (Romanos et al. 2009a), and transcranial sonography revealed structural alterations in the substantia nigra (Romanos et al. 2009b).

Environmental factors

Children with ADHD experience more frequently ante- and perinatal complications, specifically during the third trimester of pregnancy (Ben Amor et al. 2009). Furthermore, smoking during pregnancy seems to be a risk factor (Lempp et al. 2009).

It was also reported that iron levels were significantly lower in patients with ADHD, specifically in thalamic areas (Cortese et al. 2009). However, blood analyses failed to reveal significant changes in iron and ferritin levels (Caci et al. 2009).

While the role of environmental factors including nutrition and parenting styles are continuously discussed in the context of the pathogenesis of ADHD, neurobiological and genetic factors were often at the centre of interest in the studies presented. However, one of the most exciting areas in coming years will be the analysis of gene–environment interactions. This will be one of the most promising approaches when it comes to further elucidating the pathophysiological background of ADHD.

An increasingly important, but largely under-researched phenomenon consists in the ageing aspects of ADHD. R Klein (New York, USA) therefore brought the attention to the longitudinal course of ADHD through the ages and discussed the implications for diagnosis, specifically in adulthood (Klein and Mannuzza 2009). While age-dependent changes in the representation of ADHD are widely recognised, the diagnosis in adulthood remains largely a matter of debate. In an earlier study, this research team had conducted a prospective study of boys with ADHD into adulthood with a mainly forensic focus (Klein and Mannuzza 1991). The study revealed that significantly "more ADHD probands than comparisons had been arrested…, convicted…, and incarcerated" (Mannuzza et al. 2008). Obviously, "ADHD increases the risk for developing antisocial and substance use disorders in adolescence" (Mannuzza et al. 2008).

Modelling ADHD

While some aspects of ADHD and its treatment might be analysed in cell-culture models (both primary cell cultures and cell lines), only animal models allow us to investigate alterations on a behavioural as well as on a neurobiological level. Such models are typically either so-called neurotoxic (Lange 2009) or genetic models involving rodents (Gainetdinov 2009). While there are limitations in translating findings in animal models to the human condition, it is possible to investigate an important feature of ADHD, namely gene–environment interactions, as mentioned earlier (Holmes 2009; Wultsch et al. 2009).

In ADHD research, rat as well as mouse models have been used. Rat models include SHR (spontaneously hypertensive) and WKY (Wistar-Kyoto) ADHD models (Sontag et al. 2009), and mouse models are usually based on so-called knockout technology such as mice models DAT, NK1 receptor and organic cation transporter 3 (OTC3) knockouts.

Animal models can generate important information about innovative therapeutic approaches which might represent alternatives to existent treatment strategies. Based on such findings in animal models, a potential therapeutic use of red-ginseng extract and oroxylin A (a flavonoid isolated from *Scutellaria baicalensis*), both are medicinal herbs used in Korea, was suggested (Cheong et al. 2009; Shin et al. 2009). Another possible therapeutic agent might be the proline-containing dipeptide Noopept (Skrebitsky and Kondratenko 2009).

Animal models also point to an important role of NPY and its Y2 and Y4 receptors in the circadian control of locomotor, exploratory and ingestive behaviour, which might help to better understand the neurobiological basis of specific ADHD symptoms (Edelsbrunner et al. 2009).

Treatment

Pharmacology

Research into the pharmacological treatment of ADHD was one of the cornerstones of the congress. While effective pharmacological treatment for ADHD has been available for some time, there remains a plethora of important issues which need to be addressed such as the choice between stimulant and non-stimulant treatment, possible side effects, the use of long- versus short-acting drugs, the parallel treatment with non-pharmacological approaches such as psychotherapy and psycho-education, the issue of long-term treatment and treatment resistance. A growing research issue is also the quality of life under stimulant medication (Spencer et al. 2008).

Long-acting preparations of ADHD medication can considerably improve a patient's condition, but should not "replace" short-acting versions or non-stimulant pharmacological options (Banaschewski 2009). Stimulant treatment, however, does not seem to result in increased genetic toxicity (Stopper et al. 2009).

While there is considerable experience in the treatment of childhood and adolescence ADHD, data on treatment of adult patients with ADHD are still limited. As ADHD symptoms might change with ageing, treatment response can similarly undergo alterations throughout the lifetime of a patient and might therefore need modification (Fegert 2009). This also raises questions regarding treatment over a longer period of time. Long-term treatment is both safe and effective, but should involve regular monitoring of blood pressure and pulse as well as possible cardiac side effects (Konrad et al. 2009; Rosler 2009). Compared to the treatment in children and adolescents, there are two main differences in adult ADHD treatment: (1) there is a different comorbidity spectrum which should be reflected in different treatment strategies and (2) compliance can be very different: up to about 70% of adults discontinue daily stimulant medication after a few weeks and some adult patients self-medicate by adjusting the daily dosage according to their "subjective feeling of need" of stimulant medication.

While oral medication has been the traditional way of administration, there is increasing evidence that alternative systems might be very useful depending on a patient's individual situation. Transdermal systems seem to be safe and effective and may have some advantages compared to oral medication (Manos et al. 2009; Melmed et al. 2009).

In the context of "lifestyle drugs", an increasingly important issue is the use of stimulant ADHD medication by healthy individuals with the intention to "enhance" cognitive performance. However, it seems that healthy people cannot benefit from stimulant drugs in this way (Zamorski et al. 2009).

While several studies underlined the efficacy of both stimulant and non-stimulant ADHD medication, some researchers looked specifically into possible adverse effects: A case of atomoxetine-induced separation anxiety was reported (Celik et al. 2009). Disturbed sleep patterns may not improve despite ADHD medication (Khaigrekht et al. 2009).

Interestingly, doctors' prescribing behaviour for stimulant and non-stimulant drugs seems to be fundamentally different: patients receiving non-stimulant ADHD medication are significantly older, have significantly more psychosocial problems, and suffer more frequently from comorbid conditions (Wehmeier et al. 2009).

While most papers focused on main-stream treatment, positive treatment results were also reported with buspirone (Davari-Ashtiani et al. 2009) and Pycnogenol, a medication containing phenolic acids, catechin, taxi Olin and procyanidins which may act as radical scavengers and, thus, reduce oxidative-stress levels (Trebaticka et al. 2009). One study reported positive long-term effects of homeopathic treatment in ADHD children (von Ammon et al. 2009). El-Karn et al. (2009) discusses the use of repetitive transcranial magnetic stimulation in ADHD.

Positive treatment predictors for slow-release methylphenidate may be male gender, older age and lower educational level (Trott et al. 2009).

Kratchovil summarised current pharmacotherapeutic options for ADHD. In earlier studies, he and his team had already shown the efficacy of both methylphenidate and atomoxetine (Kratochvil et al. 2003). Stimulant as well as non-stimulant treatment is not only useful in the treatment of children and adolescent, but is also an important option in the therapy of adult patients. He concludes that pharmacotherapy "can be a safe and effective aspect of the treatment plan for some adults with ADHD" (Kratochvil 2009).

Stopper et al. (2009) found that chronically treatment with methylphenidate does not increase genomic damage, concluding that psychostimulants do not seem to induce genetoxicity.

Squires et al. (2009) showed that lisdexamfetamine exhibited significant efficacy versus placebo in the control of ADHD symptoms in children. Adverse events are reduced appetite, insomnia and headache. The authors conclude that lisdexamfetamine can significantly improve ADHD symptoms, while being generally well tolerated (Squires et al. 2009).

Yang and co-workers investigated the impact of Atomoxetine on executive function, and conclude that this medication might have a positive impact on working memory, set shifting, planning and inhibition in children (Yang et al. 2009).

Non-pharmacological treatment strategies

While there might often be a displace between research into psychopharmacology and studies about non-pharmacological treatment strategies, the organisers of the congress encouraged the presentation of scientific data analysing psychotherapeutic, psycho-educative and other approaches. Group-based dialectical behavioural therapy is an effective and well-tolerated treatment in adult patients with ADHD and can be combined with pharmacotherapy (Haaparanta et al. 2009; Hirvikoski et al. 2009). Parent training seems to be especially helpful in severe cases (Hautmann et al. 2009), and there are specific psycho-educational aids available (Preuss et al. 2009). The use and usefulness of several specific non-pharmacological treatment programmes was reported by various different groups (Czyewski et al. 2009; Lafleur et al. 2009; Masse et al. 2009; Montoya and Ferrin 2009; Paul et al. 2009; Rouleau et al. 2009). In adult patients with ADHD, intense physical exercise might be useful (Winter et al. 2009).

Forensic and social aspects

ADHD, specifically in adults, has important forensic implications. The two main forensic issues are (1) whether (and if so to what extent) ADHD should be considered as a mitigating factor in persecuting delinquent behaviour, and (2) how ADHD should be managed in offenders (Hay 2009). ADHD clearly is a predisposing factor for several forms of delinquent behaviour such as risky and erratic driving (Retz 2009; Rohde 2009a, b). While it has been shown in several previous studies that there is an association between ADHD and delinquent behaviour in men, the prevalence of ADHD seems to be high among female prison inmates (Konstenius et al. 2009).

Apart from such forensic implications, the quality of life in patients with ADHD as measured by standardised questionnaires is significantly diminished (Yildiz Oc et al. 2009). Furthermore, transcultural and gender-specific differences remain challenging issues in ADHD diagnosis and treatment (Couture and Masse 2009; Haußinger et al. 2009; Osmancevic et al. 2009; Radmanovic et al. 2009).

Conclusion

The 2nd International Congress on ADHD, From Childhood to Adult Disease, held on 21–24 May in Vienna, brought together a worldwide audience of scientists, physicians, and representatives of patients and their families as well as other stakeholders. There was a special emphasis that ADHD does not only affect children and adolescents, but that adult ADHD is a worldwide health problem which

urgently needs to be addressed. The research papers covered a wide spectrum of ADHD-related issues, documenting both the immense scientific progress made in recent years, but also the great need for further research efforts. As such this conference represents a unique and indispensable international forum for the ADHD community.

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