Neurodevelopmental disorders such as attention deficit hyperactivity disorder and autism represent a significant economic burden, which justify vigorous research to uncover its genetics and developmental clinics for a diagnostic workup. The urgency of addressing attention deficit hyperactivity disorder comorbidities is seen in the chilling fact that attention deficit hyperactivity disorder (ADHD), mood disorders, substance use disorders and obesity each increase the risk for mortality. However, data about comorbidity is mainly descriptive, with mechanistic studies limited to genetic epidemiological studies that document shared genetic risk factors among these conditions. Autism and intellectual disability affects 1.5 to 2% of the population in Western countries with many individuals displaying social-emotional agnosia and having difficulty in forming attachments and relationships. Underlying mechanisms include: (i) dysfunctions of neuronal miRNAs; (ii) deletions in the chromosome 21, subtelomeric deletions, duplications and a maternally inherited duplication of the chromosome region 15q11-q13; (iii) microdeletions in on the long (q) arm of the chromosome in a region designated q21.1 increases the risk of delayed development, intellectual disability, physical abnormalities, and neurological and psychiatric problems associated with autism, schizophrenia, and epilepsy and weak muscle tone (hypotonia); (iv) interstitial duplications encompassing 16p13.11.

Keywords: ADHD, comorbidities, obesity, autism, intellectual disability, genetics.
not seen in obese subjects. Resembling the blunted amphetamine response, dopamine release after a meal was strong correlated with body mass index (BMI). Likewise, a carbohydrate rich meal was associated with increases in dopamine in normal weight individuals but with decreases in obese participants [15]. While aerobic exercise is known to modulate body weight, it is becoming increasingly that exercise also has a potential role in combating drug addiction [16]. The efficacy of exercise in drug use appears to rely upon its interference with dopaminergic neurotransmission. At gene level, mouse lines bred for hyperactivity and obesity both exhibit differential gene expression relevant to the function of dopamine system [17]. Importantly, aerobic exercise also increases the efficacy of methylphenidate in ADHD [18]. Importantly, exercise alleviated hyperactivity along with increasing dopamine system [17]. Importantly, aerobic exercise also increases the efficacy of methylphenidate in ADHD [18].

Alterations in the circadian system

Circadian rhythms are driven by CLOCK genes and their interaction with external ‘zeitgebers’ such as light, food intake, and physical activity/exercise. Circadian rhythms sleep and CLOCK genes form another pathophysiologically link between ADHD and its comorbidities: disturbed circadian rhythm and altered sleep are a key feature of ADHD [20, 21]. CLOCK genes regulate weight changes, especially of obese patients, and obesity in turn alters the circadian expression of CLOCK genes. The importance of altered circadian rhythms in mood disorders is well established, and there is a close link between circadian CLOCKs and mood-related behaviors. Finally, both anxiety disorders and substance use disorders (SUDs) have been linked to CLOCK genes. ADHD medication often improves sleep efficiency and can specifically alter CLOCK gene expression [19]. Therefore, insight into the alterations of circadian rhythms in ADHD and its relation to the comorbidities opens up the perspective of novel therapeutic modulation of biological systems.

Disturbances in the circadian rhythm may have dramatic effects on our health. Circadian rhythms abnormalities are associated with key and common psychiatric conditions, such as mood disorders. As circadian disturbances are at the core of depression, normalizing circadian rhythm may be a fruitful avenue for new therapeutic targets in depression [22, 23]. The circadian system ensures the generation and maintenance of self-sustained, ~24-hour oscillations in physiological and behavioral processes that are linked to internal and environmental changes, predominantly by daily changes in light intensity. Circadian rhythms are sustained at the molecular level by a series of interconnected transcription–translation feedback loops that control the expression of clock genes comprising the molecular circadian clock [24]. The rhythm signals propagated from suprachiasmatic nuclei are subject to a transcriptional–translational feedback loop provided by core clock genes including CLOCK (circadian locomotor output cycles kaput), BMAL (brain and muscle ARNT-like-1), PER (period) and CRY (cryptochrome), and orphan nuclear hormone receptors REV-ERB alpha (encoded by Nrl1) and Ror alpha. The circadian expression of these genes is regulated through E/E boxes (CACGTG/CACGTT sequence), REV-ERB alpha/ROR (retinoic acid-related orphan receptor) response element (RRE), and DBP/E4BP4 binding element (D box) in their promoter regions.

First, the CLOCK and BMAL proteins dimerize and bind to E-boxes present in the promoter region of period genes (Per1, Per2, and Per3) and cryptochrome genes (Cry1 and Cry2) to induce their expression. Subsequently, the PER and CRY proteins form a repressor complex in the cytoplasm and relocate to the nucleus where they inhibit the genes induced by the CLOCK/BMAL protein complex, including their own transcription, forming a negative feedback loop. The cycle restarts approximately 24 hours later, upon degradation of PER proteins. Additional interlocking loops involve clock-controlled transcription factors such as D site of albumin promoter (DBP) and REV-ERBa whose expression is primarily activated by the CLOCK:BMAL1 heterodimer. REV-ERBa represses Bmal1 transcription by directly binding to the ROR elements (ROREs) in the Bmal1 promoter, which adds robustness to the clock. However, the ROR/REV/Bmal1 loop was not found to be necessary for basic clock function, its plausible role is to control rhythmic transcription of clock output genes [25].

Circadian dysfunction in ADHD

Chronic sleep-onset insomnia has been shown to be associated with childhood and adult ADHD. In ADHD children, sleep onset insomnia has been associated with a phase delay in the Dim Light Melatonin Onset (DLMO). Such a phase delay in the DLMO has recently also been reported in adult ADHD patients with chronic sleep onset insomnia [26]. ADHD is associated with changes in diurnal preference towards greater eveningness. Abnormal circadian melatonin secretion has been associated with childhood and adult ADHD. Baird et al. [20] recently examined for the first time circadian rhythmicity simultaneously at the molecular, endocrine and behavioral levels in adults with ADHD as well as age- and sex-matched controls. Circadian rhythms were measured by means of actigraphy, by self-sampling of oral mucosa for assessment of rhythmic expression of the clock genes BMAL1 and PER2, and by estimation of salivary mucosa and melatonin levels. BMAL1 and PER2 showed circadian rhythmicity in controls with this being lost in the ADHD group. Cortisol rhythms were significantly phase delayed in the ADHD group. These findings indicate that adult ADHD is associated with a circadian desynchrony that in turn may lead to decreased sleep duration and quality.

Non-pharmacological approaches in ADHD: bright light therapy and physical activity

Against the background of a substantial circadian dysfunction in children and adults with ADHD, first studies have examined the potential of chronotherapeutic approaches such as light therapy (LT) in ADHD and explored the effect of ADHD medications upon the circadian clock. LT has evolved as a non-invasive agent for the treatment of seasonal affective disorder and more recently for major depressive disorder as well. LT is safe, cost-effective and high patient compliant. Physiologically,
when administered in the early morning. LT has been shown to have an effect by suppressing melatonin production and thereby advancing circadian rhythms. Moreover, morning exposure to bright light decreases cortisol levels that usually peak after waking-up. Hence, with morning light administration, timing of sleep can be shifted, and circadian rhythms can be stabilized. Three weeks of LT morning bright LT in 29 ADHD adults were associated with a significant reduction in both subjective and objective measures of core ADHD pathology, with the strongest predictor of improvement being phase advances of the circadian rhythm [27].

Exercise and physical activity have well known health benefits. Physical therapy increases plasma brain-derived neurotrophic factor (BDNF) levels in non-frail and pre-frail elderly women suggests that BDNF may not only be a marker of frailty but could play a relevant neuroprotective role in the context of frailty syndrome [28]. Mechanistically, exercise is associated with increased levels of serum BDNF enhanced hippocampal neurogenesis, monoamine neurotransmission and synaptic growth [29]. BDNF is thought to mediate exercise-related neuroplasticity [30] and is a potential biological moderator or mediator of antidepressant response [31].

Exercise is efficacious as a monotherapy [32, 33] as well as in combination with other treatments for depression [34] when used as a first step treatment. For mental disorders, the therapeutic effects of exercise have also been described for anxiety disorders but also for dementia and mild cognitive impairment. It is thought that physical activity releases dopamine in the brain improving attention and cognition and therefore may be used to regulate hyperactivity, and improve concentration in patients with ADHD (Figure 1).

**Figure 1 – ADHD and autism may be caused by various factors: genetic, environmental or comorbidities.**

Polymorphisms in molecular clock genes not only show an association with the disorder but also seem to influence response to treatment and symptomatology characteristics. Melatonin levels are reported to be suppressed in bipolar disorder, with phase advances of the melatonin rhythm associated with mania and phase delays with depressive episodes or euthymia [35].

Since Brown et al. [36] demonstrated that primary cells from skin biopsies are ideal for surrogate measurements for assessing circadian phenotypes, a number of subsequent studies done in patients have confirmed the potential use of fibroblast explants to examine circadian rhythms and clock gene expression in insomnia and psychiatric disorders [37].

An estimated 4.4% of the adult population suffers from ADHD, with over 70% of these individuals experiencing insomnia. Even groups of ADHD subjects who do not report sleep problems often manifest clinically significant insomnia [38]. Although converging evidence shows that the dopamine system (DA) and circadian rhythm (CIRCA) dysregulation predispose to co-morbidity, the present state of knowledge largely relies on small studies. Exogenous melatonin is commonly used to treat insomnia in ADHD, but study results regarding its efficacy are conflicting [39]. Another study of chronobiological treatments for ADHD demonstrated that advancing the circadian phase in ADHD subjects by use of morning bright light therapy is strongly correlated with improvement in core ADHD symptoms [27]. However, this study has not been replicated with objective measures of circadian phase. Chronobiological treatments, such as bright light therapy and are gaining momentum with the use of total sleep deprivation to advance circadian phase in manic bipolar subjects in order to stabilize mood [40].

**Autism and mental retardation**

Intellectual disability affects 1.5 to 2% of the population in Western countries [41]. Intellectual disability is one of the main causes of handicap and is characterized by impaired intellectual functioning and repetitive and restricted interests and behavior as expressed in conceptual, social and practical adaptive skills originating in the first three years of infancy and last throughout adulthood. Many individuals with autism display social-emotional agnosia and have difficulty in forming attachments and relationships.

Autism spectrum disorders with symptoms ranging from mild to severe forms have been estimated to affect as many as one in 100 to one in 150 children [42, 43]. Autism is characterized by marked difficulties in behavior, impaired social relationships, difficulty in perceiving the emotional state of others, or even expressing emotions. Also, there are autistic people who speak fluently, others who are speech impaired. Many individuals with autism spectrum disorders have significant limitations in intellectual functioning, and need substantial social and educational support. Therefore, autism and intellectual disability together represent a significant economic burden, which justify vigorous research to uncover its genetics and developmental clinics for a diagnostic workup.

Intensive investigations during the past decade have established connection between structural chromosomal abnormalities and autism spectrum disorder (ASD) phenotypes and led to the discovery of chromosomal copy-number changes and single-nucleotide changes in patients with intellectual disability and autism. However, the vast majority of subjects do not have a genetic diagnosis that would allow a prediction of recurrence risk to the family and a better management of the disease. MicroRNAs (miRNAs) are small endogenous RNA molecules that can simultaneously influence the expression of multiple genes at post-transcriptional level.

It has become increasingly evident that dysfunctions of neuronal miRNAs influence the pathogenicity of genomic changes. A recently published study highlighted that miRNAs
are components of both the genetic architecture as well as biological pathways that mediate the effects of primary genetic deficits in autism. Five miRNAs were previously reported in ASD and three of them were required for neuronal function [44]. Study has reported that three (miRNA-7, miRNA-9, miRNA-106b) out of 84 miRNAs were associated with neurodegenerative disorders and one with intellectual disability (miRNA-9) [45–47]. Altogether, these data suggest a possible role of miRNA copy-number change in cognition and/or copy-number variation (CNV)-mediated developmental delay.

The Down syndrome is a developmental disorder that was the first recognized as a cause of intellectual disability due to changes in chromosomal copy-number and was caused by an extra-copy of chromosome 21 [48]. Now it is firmly established that some patients with intellectual disability also had deletions in the chromosome 21, subtelomeric deletions, duplications and a maternally inherited duplication of the chromosomal region 15q11-q13 [49–52]. Likewise 1q21.1 microdeletion occurs some 21, subtelomeric deletions, duplications and a mater

Now it is firmly established that some patients with variation (CNV)-mediated developmental delay. Altogether, these data suggest a possible role of miRNA (miRNA-7, miRNA-9, miRNA-106b) out of 84 miRNAs were associated with neurodegenerative disorders and one with intellectual disability (miRNA-9) [45–47]. Altogether, these data suggest a possible role of miRNA copy-number change in cognition and/or copy-number variation (CNV)-mediated developmental delay.

Conclusions

The urgency of addressing ADHD’s comorbidities is seen in the chilling fact that ADHD, mood disorders, SUDs and obesity each increase the risk for mortality. However, underlying mechanistic studies are lacking. Autism and intellectual disability together represent a significant economic burden, which justify vigorous research to uncover its genetics and developmental clinics for a diagnostic workup. Underlying mechanisms include: (i) dysfunctions of neuronal miRNAs; (ii) deletions in the chromosome 21, subtelomeric deletions, duplications and a maternally inherited duplication of the chromosomal region 15q11-q13; (iii) microdeletions in the long (q) arm of the chromosome in a region designated q21.1 increases the risk of delayed development, intellectual disability, physical abnormalities, and neurological and psychiatric problems associated with autism, schizophrenia, and epilepsy and weak muscle tone (hypotonia); (iv) interstitial duplications encompassing 16p13.11.

Conflict of interests

The authors declare that they have no conflict of interests.

References


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