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Commentary

Wake up to the benefits of timely management of sleep problems in toddlers with Williams Syndrome

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This commentary relates to Gwilliam, Joyce, and Dimitriou [1] and their longitudinal work on sleep problems in toddlers with Williams syndrome (WS). WS is a rare and sporadic genetic disorder caused by a small deletion of genes on chromosome 7 [2]. Individuals with WS experience a range of medical and developmental difficulties and sleep disturbances are highly prevalent. The aim, here, is to address why early identification of sleep problems could be beneficial for children with WS and their families. The specific sleep difficulties reported in children with WS will be outlined and the importance of early, syndrome-specific sleep support will be discussed, with reference to clinical outcomes.

Sleep plays a fundamental role in healthy development and promotes optimal cognitive and daytime functioning. Sleep disturbances are associated with a range of negative outcomes. For children with typical development (TD), these include compromised cognitive functioning, increased behavioral problems and emotional dysregulation [3,4]. For children with neurodevelopmental disorders, it is probable that sleep difficulties compound their existing functioning difficulties; described by Owens [5] (p. 541) as a 'double jeopardy'.

In TD, early sleep difficulties are predictive of future disturbances [6]; Yet, implementing early and brief sleep interventions has been reported to have a high success rate for improving sleep outcomes [7,8]. Treating sleep problems also provides demonstrable benefits for cognitive and behavioral functioning, with even moderate improvements in sleep patterns resulting in improved functioning [9,10]. Conversely, modest sleep debt on a regular basis may result in children becoming chronically sleep deprived, which can affect development [11]. Furthermore, longitudinal studies have revealed that there is an association between sleep in early childhood and cognitive and behavioral functioning at school age [12,13]. Crucially, the relationship between sleep and cognitive functioning appears to intensify over time [11]. This provides strong evidence that treating sleep problems as early as possible will minimize the adverse effects of sleep loss on functioning and long-term development.

In TD, almost a third of children experience sleep difficulties in the pre-school years [14,15]. Sleep patterns change with age and follow a distinct developmental trajectory. By school-age, there is a reduction in reported sleep difficulties; although these remain for almost one fifth of children [16]. In general, by school-age, sleep quality is improved and total sleep duration is shorter, but notably, more consolidated.

For children with WS, the developmental trajectory of sleep difficulties presents differently. Growing evidence indicates that sleep problems emerge as early as the toddler years, with parent-reported short sleep durations and long settling times [17,18]. Objective measures corroborate this and worryingly, unlike in TD, there is no indication of maturational improvement [1]. Thus, where sleep problems tend to be transient in TD, they become chronic in WS; Sleep difficulties emerge in early childhood, remain common at school-age, manifesting in short sleep durations, bedtime resistance, long sleep latencies and frequent night waking [19] and persist into adulthood [20]. Consequently, there is a high prevalence of individuals with WS experiencing sleep difficulties throughout life, which is reflected in the inclusion of *sleep issues* in the official clinical guidelines for the management of Williams Syndrome [21].

It is unknown as to what extent sleep disturbances may contribute to the range of cognitive and behavioral difficulties associated with WS, which include mild to moderate intellectual disability, visuo-spatial difficulties, poor executive functioning, attention problems and high levels of anxiety [22-24]. The specific interplay between both sleep & cognition, and sleep & behavior, remains unclear, with bidirectionality a distinct possibility. Studies are increasingly linking sleep disturbances with functioning difficulties in children with developmental disorders or those with an intellectual disability [25-27]; more frequent and severe sleep problems are associated with greater cognitive and behavioral difficulties [26]. Thus, it is feasible that there is an additive effect of sleep problems on functioning difficulties for individuals with WS, and, by treating sleep difficulties there is the potential to improve cognitive and behavioral outcomes.

de Magalhaes G, et al. [28] explored the associations between sleep and language development and behavior problems in 2-year-olds with WS. Night-time sleep duration was positively associated with language development [28], consistent with other findings [18,29]. Previous studies have examined the link between sleep disturbances and behavioral problems in children with WS but no significant associations were observed [18,30]. In contrast, de Magalhaes G, et al. [28] found that, in addition to a high proportion of children with WS experiencing behavioral difficulties, problems were significantly greater for children who screened positive for a Sleep-Related Breathing Disorder or excessive daytime tiredness. The authors proposed that the demonstrable link highlights the importance of assessing sleep problems early in life as they could contribute to, or exacerbate, behavior problems.

Functioning difficulties are not the only concern associated with sleep problems. There are potential health risks associated with poor sleep in children, including in the cardiovascular and immune systems [5]. This could be of particular concern in the WS population, as cardiovascular disease is present in approximately 84% of cases.

Furthermore, sleep disruption also impacts wider family life. Meltzer and Montgomery-Downs [31] highlighted the importance of viewing children's sleep problems within a family context. Often there is a direct relationship between childhood sleep problems and quality and quantity of parental sleep [5]; compromising parental daytime functioning and increasing the risk of parental stress, mood and quality of life [32]. This potential is certainly present for parents of toddlers with WS, who reported high levels of involvement in their child's sleep and frequently viewed it to be problematic, yet received limited professional support [1]. Feasibly, due to professionals lacking knowledge about WS, a source of stress for parents of children with WS [33]. Practitioner knowledge is crucial for sleep support as parents may not appreciate the extent to which untreated sleep problems will negatively impact multiple facets of their child's development.

A growing body of research is demonstrating that genetic disorders, such as WS, have their own unique sleep profile, with potentially differing causal mechanisms [17,34]. This indicates that despite sleep problems displaying common features, such as frequent night waking or bedtime resistance, it is likely that the nature of sleep problems are varied. This recognition is the first step in providing syndrome-specific sleep support but, consequently, treating sleep difficulties is more complex than it may appear. Generalizing sleep management from the TD population will not be applicable for individuals with WS. A thorough understanding of the unique features and individual sleep profile of WS is required. Without this, health professionals will not have the necessary tools to effectively manage and treat sleep difficulties.

Mason et al. [30] suggested that a behavioral intervention could be considered for managing and treating sleep difficulties in WS. By promoting good sleep hygiene, more specifically a consistent bedtime routine, they proposed that self-soothing skills might improve, increasing sleep efficiency. Arguably, positive sleep hygiene should always be used as a first line of treatment because, even if measures are not sufficient to treat sleep problems, success of other interventions would be limited if poor sleep habits are not addressed [35,36]. A recent review exploring the effectiveness of behavioral sleep interventions on treating sleep problems in rare genetic neurodevelopmental disorders, including WS, found some positive treatment effects but highlighted the need for more studies in the area [37].

In conjunction with behavioral measures, pharmacological management of sleep difficulties in children with WS could be considered and has had some success. Martens et al. [38] identified that, from a large sample of individuals with WS (513), a quarter had taken medication to help with sleep, at some stage. Melatonin was the most commonly used medication and it was widely reported to be helpful (91%). Further evidence is needed to determine in what ways it was helpful; most likely it would improve sleep onset difficulties but the impact on sleep duration and night waking requires more exploration. Furthermore, increased levels of respiratory-related arousals in children with WS could indicate an intrinsic sleep-disrupter, such as obstructive sleep apnea [30]; overnight polysomnography could be appropriate to screen for problems and specific treatment, such as assessment for adenotonsillectomy, could be required.

Longitudinal studies are needed to assess the effectiveness of any management of sleep problems in WS. This would also help address our ability to determine whether treating sleep difficulties in the early years could affect the developmental sleep trajectory in WS, and, in what ways this might subsequently impact development.

In summary, our understanding of the individual WS sleep profile is growing. The recent evidence identifying sleep problems to be present in toddlers with WS demands attention. The pre-school years constitute a period of rapid cognitive and behavioral development, reflected in huge anatomical and physiological brain growth [39]. Not only could sleep disturbances confound existing functioning difficulties, but age will likely magnify effects. Thus, management of sleep problems at an early age, using a targeted and syndrome-specific approach, will lead to a greater opportunity for maximizing children's developmental potential and improving clinical outcomes, as well as enhancing quality of life for the entire family.

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