

Neuropsychiatric Disorders and Voiding Problems in Children

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Abstract In the literature, it is well documented that children who have daytime incontinence issues have a higher chance of having some form of behavioral or learning problem. It has been speculated that these issues may be related to their incontinence. On the other hand correction of the central nervous system problem may make these wetting problems disappear. We explore the most recent literature in functional imaging of the brain and the relationship between inherited neuropsychiatric problems and daytime wetting. The findings appear to dispel the aforementioned conclusions and tend to support an inherited or at least an altered developmental pathway for the development of daytime wetting issues.

Keywords Voiding dysfunction · Wetting · Neuropsychiatric disorders · Central nervous system · Genetics · Lower urinary tract symptoms · Incontinence · Attention deficit hyperactivity disorder · Schizophrenia · Depression · Anxiety · Cortical thickness · Pediatrics

Introduction

It has been well described in the literature that voiding and incontinence problems are commonly associated with behavioral and developmental problems. For years, we have known that patients with attention deficit disorder and attention deficit hyperactivity disorder (ADHD) were more difficult to treat than other children with incontinence or lower urinary tract symptoms (LUTS). After careful

observation of our patients over an extended period of time, we have begun to recognize that there is an increased association between other neuropsychiatric disorders and LUTS. We also found that it was clear that the patient did not have to carry a diagnosis of a neuropsychiatric disorder, but as long as a family member had an issue, they could put that child at risk, the same as if the child had a diagnosis of a neuropsychiatric disorder. We have found this phenomenon repeated in several studies that we have conducted in children, from patients with urgency/frequency syndrome to those who have autonomic dysfunction. Is there some connection between these neuropsychiatric disorders and LUTS in children? Examination of the psychiatric literature has revealed some very interesting studies that may help explain our findings and further tie together the association between two seemingly disparate problems.

Neuropsychiatric Diseases and Voiding Issues

Children with elimination disorders have an increased rate of comorbid behavioral or psychological disorders. About 20–40% of children with daytime urinary incontinence are affected by comorbid behavioral disorders [1, 2]. In a large epidemiological study of a cohort of 8213 children aged 7.5–9 years, children with daytime wetting had significantly increased rates of psychological problems, especially separation anxiety (11.4%), attention deficit (24.8%), oppositional behavior (10.9%), and conduct problems (11.8%) [3]. In the same cohort, 10,000 children aged 4–9 years were analyzed. Delayed development, difficult temperament, and maternal depression/anxiety were associated with daytime wetting and soiling [4]. In another population-based study that included 2856 children, the incidence of incontinence was 16.9% within the previous

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6 months [5]. In a retrospective study of patients with ADHD, 20.9% wetted at night and 6.5% wetted during the day. The odds ratios were 2.7 and 4.5 times higher, respectively, which means that there is unspecific association of ADHD and both nighttime and daytime wetting [6]. Of 140 children with ADHD, 25% were affected by nocturnal enuresis compared to 10.8% of 120 control patients. The highest comorbidity rates of 40% for ADHD and nocturnal enuresis were reported by Baeyens et al. [7], possibly due to selection effects. In this study, 15% had a combined type of ADHD, 22.5% had an inattentive type, and only 2.5% had a hyperactive type. In a community-based sample, the prevalence rate was much lower [8]. ADHD continued to be present in 72.5% of children in a 2-year follow-up, indicating a high stability [8]. Children with ADHD continued to wet at follow-up much more often (65%) than control patients (37%; OR: 3.17) [8]. At a 4-year follow-up, 64% still had ADHD. Of these, 42% continued to wet at night (compared to 39% of the control patients) [9].

Of possible elimination disorders, children with fecal incontinence (or encopresis) have the highest rates of comorbid behavioral disorders: 30–50% of all children have clinically relevant behavioral disturbances [1, 2]. In a recent epidemiological study of over 8242 7- to 8-year-old children, a wide range of comorbid Diagnostic and Statistical Manual of Mental Disorders, 4th edition disorders were significantly increased: separation anxiety (4.3%), social phobias (1.7%), specific phobias (4.3%), generalized anxiety (3.4%), depressive disorders (2.6%), ADHD (9.2%), and oppositional defiant behavior (11.9%).

Of all types of functional elimination disorders, children with nocturnal enuresis have the lowest rate of comorbid disorders; 20–30% are affected. This rate is still significantly increased compared to nonwetting control patients. Also, comorbidity rates differ regarding subtypes of nocturnal enuresis.

In a study by Bael et al. [10] in 2008, they found that, before treatment of non-neurogenic bladder sphincter dysfunction (NNBSD) in the European bladder dysfunction group, behavioral problems were present in 19% of the children at a rate of 2:1 compared to normative population. After treatment of incontinence, the rate dropped to 11%, which was the same as the normative group. The treatment was primarily behavioral therapy and biofeedback. This significant change in score was seen only in the dysfunctional voiders and did not change at all in the patients who had urge syndrome. Conventional wisdom would implicate the bladder as the source of the behavioral problems in the urge group. The dysfunctional voiders who did respond with resolution of their voiding issues seemed to be put at ease and their behavioral problems resolved. Interesting to note is that there still were patients that persisted with

behavioral problems after the dysfunctional issues had been settled. A better explanation based on a neurocentric way of thinking would implicate the lack of change in the behavior of these patients to a central defect in the ACG or prefrontal cortex (PFC) that has given them the behavioral problems, regardless of the outcome of their LUTS, and there should be no expectation that their underlying neuropsychiatric issues would improve with correction of the LUTS. On the other hand, the patients with voiding dysfunction could benefit from a bowel program and biofeedback if their problems were due to learned aberrant behavior, and correction of such behavior could lead to resolution of their LUTS as well as some behavioral issues due to the LUTS. It also can be explained that in some of the patients with dysfunctional voiding, their behavior did not improve, and in this group, voiding dysfunction was most likely linked to the PFC/ACG problem.

The association of urinary incontinence and lower psychological well-being in adults also has been noted by Botlero et al. [11]. Major depression can predict the onset of urinary incontinence in women in an at-risk population-based sample [12]. One study found increased rates of enuresis in adult bipolar disorder (18%) [13]. There also has been an association with panic disorder and interstitial cystitis that has been described in the literature [14]. A publication in 1990 revealed that patients that were described as having psychoneuroticism were less likely to respond to treatment of detrusor instability than those who had no form of psychoneuroticism. Most good responders and one third of nonresponders were free of psychiatric issues [15]. Of important note is that 25% of the patients in this study had IBS symptoms. These findings were no different than our data that indicate that patients with urge syndrome who are nonresponders have a 50% chance of having some form of neuropsychiatric problem. Enuresis also was found to be a premorbid developmental marker for schizophrenia (SCZ) [16••]. The authors found that patients with SCZ had higher rates of childhood enuresis (21%) compared with siblings (11%) or control patients (7%), and the relative risk for enuresis was increased in siblings. Patients with enuresis performed worse on two frontal lobe cognitive tests (letter fluency and category fluency) as compared with nonenuretic patients. What is noteworthy is that cerebral defects associated with these disorders tend to cluster around the ACG and PFC, which is exactly where the defects are being seen in patients with urgency and urge incontinence.

Cortical Thinning and Neuropsychiatric Disorders

The same study that looked at patients with SCZ and incontinence also looked at the brains of these patients

along with those of the siblings and control patients [16••]. It was found that the voxel-based mapping (VBM) analysis of probands revealed frontal grey matter decreases in those with a history of enuresis (16 probands with enuresis and 66 probands without enuresis); specifically, reductions of grey matter volume in the right superior frontal gyrus (BA 9), right middle frontal gyrus (BA 10), bilateral inferior frontal gyrus (BA 45), and right superior parietal cortex (BA 7). The VBM analysis of the subset of healthy control patients also revealed areas of significantly decreased grey matter volume in those with a history of enuresis (11 healthy control patients with enuresis and 91 healthy control patients without enuresis). More specifically, they found reductions of grey matter volume in the right medial frontal gyrus (BA 11), right middle temporal gyrus (BA 21), left middle temporal gyrus (BA 22), and left cuneus.

Work by Petersen et al. [17••] performed on families at risk for depression looked to cortical imaging to try to find a link between a high-risk group of patients that had moderate to severe, recurrent, and functionally debilitating major depressive disorder (MDD) and a control group composed of a sample of matched adults from the same community who had no discernible lifetime history of depression. Maps of cortical thickness demonstrated broad expanses of statistically significant thinning in the lateral aspect of the right hemisphere in the high-risk group, including the inferior and middle frontal gyri; the somatosensory and motor cortices; the dorsal and inferior parietal regions; the inferior occipital gyrus; and the posterior temporal cortex. Thinning was absent in the lateral aspect of the left hemisphere of the high-risk group. Areas of statistically significant cortical thickening in the high-risk group were detected in the subgenual cortex, anterior and posterior cingulate gyri, and medial orbitofrontal cortex of the right hemisphere. Findings were similar in analyses of children and adults separately, and no interaction of age with risk group was detected. Analyses of cortical volumes revealed regional differences across groups that were similar to those detected using measures of cortical thickness. Although cortical thickness was not associated with a lifetime history of MDD or anxiety disorder, cortical thickness did correlate significantly with the severity of depression and anxiety symptoms at the time of scan, but primarily in the left rather than in the right hemisphere. The impressive thinning of the cortical mantle in the right hemisphere of the high-risk group compared with the low-risk group, and its independence both from a prior history of MDD or anxiety disorder and from current depressive or anxiety symptoms, naturally raise the questions of what the functional consequences of the cortical thinning may be and how those functional consequences may increase the risk for developing MDD or anxiety.

Interestingly, right superior frontal damage has been associated with transient urinary incontinence in adulthood [18]. In adult patients with SCZ, Hyde et al. [16••] found that decreased volume of the right superior frontal gyrus was associated with persistent, yet ultimately transient, urinary incontinence in childhood. This finding suggests that, at least in patients with SCZ, delayed or abnormal development of the right superior frontal gyrus (BA 9) may mediate childhood enuresis. The VBM analysis on adult probands revealed that a childhood history of enuresis was associated with decreased grey matter in several frontal (right BA 9, right BA 10, bilateral BA 45) and one parietal region (right BA 7). In control patients, a somewhat different pattern emerged, with decreased grey matter in frontal (right BA 11) and temporal (right BA 21, left BA 22) cortices and the left cuneus. Lesion studies have associated acquired frontal lobe lesions in adulthood with the development of urinary incontinence [19]. The findings from patients with SCZ and control patients are in agreement with the proposition that the frontal lobes are intimately involved in the development and maintenance of volitional bladder control. The fact that these structural differences are present in adults with no current incontinence but a childhood history of enuresis suggests that they represent vestigial developmental pathology that is functionally compensated.

The common finding among children that they wet without knowing can be accounted for by findings in the work by Peterson et al. [17••]. They postulated that because the right cerebral hemisphere is thought to be dominant in mediating certain forms of attention and visuospatial memory [20, 21]. They assessed the correlations of cortical thickness with measures of inattention and visual memory. Both measures correlated with cortical thickness more strongly and over a larger spatial extent in the right hemisphere than in the left in each risk group individually and in both groups together. Thinner cortices in the right hemisphere were associated with greater degrees of inattention and with poorer performance on immediate and delayed visual memory tasks, even though measures of inattention and visual memory were not themselves significantly intercorrelated. The correlations of cortical thickness with measures of inattention and visual memory, together with the thinner cortices detected in the high-risk group, predicted that the high-risk group would report significantly more inattentiveness and would score lower on measures of visual memory than would the low-risk group, and this group difference, in fact, is what they found. The possibility that cortical thinning of the right hemisphere could produce inattention for social and emotional stimuli, and that inattention to social stimuli could produce depressive symptoms or MDD, predicted that the degree of inattentiveness in the sample could account for a

significant proportion of the lifetime rates of MDD and anxiety disorder. These analyses demonstrated that cortical thickness significantly mediated the association of familial risk status with scores for both inattention and visual memory, effects that were by far most prominent in the right hemisphere and in the same regions where they detected the associations of cortical thickness with risk status. Furthermore, they found modest evidence that inattention, but not visual memory scores, mediated the relationship of cortical thickness with the severity of MDD and anxiety symptoms. These findings strongly suggest that the predisposition to familial depression derives from disturbances of cortical grey matter in the right cerebral hemisphere. The 28% average reduction in cortical thickness of the right hemisphere is remarkable for its magnitude and spatial extent, rivaling the magnitude and extent of cortical morphological abnormalities reported in the most severe neuropsychiatric disorders, including SCZ and Alzheimer's diseases [22, 23•], and is perhaps all the more remarkable given that the thinning is present even in persons who have never suffered from MDD or anxiety disorder but who are biological descendants of a relative with depression. The presence of the findings in individuals with and without a prior lifetime history of depression who were at increased familial risk for MDD suggests that these abnormalities are not simply a consequence of previously having been depressed or having been treated for depression. Rather, the findings suggest that thinning of the cortical mantle in the right hemisphere probably constitutes familial trait vulnerability for the development of MDD. The presence of the findings across a wide age range, the presence of the findings in children of the sample when analyzed separately, the absence of an interaction of age with risk group, and the increased rates of anxiety disorders and MDD in childhood and adolescence that have been documented previously in this cohort [24] suggest that the determinants of the cortical thinning probably are operative early in development, either in utero or during early childhood. The concept of persistence of structural abnormalities in the adult brain related to early postnatal motor development previously has been reported with respect to infant motor development. Ridler et al. [25] found that, in normal control patients, the earlier the age of learning to stand and walk, the greater the grey matter volumes in the premotor cortex, caudate nucleus, thalamus, and cerebellum in adulthood. These findings are similar to the work by Hyde et al. [16••], but the Ridler et al. [25] study was notable for demonstrating continuity between behavioral markers of early postnatal development and adult brain structure in humans. Moreover, Ridler and colleagues [25] found that patients with SCZ not only had significant delays in early motor development, but also had abnormal associations between early motor development scores and

adult premotor cortical grey and frontoparietal white matter volumes. Similarly, Hyde et al. [16••] found that patients with delayed acquisition of urinary continence had smaller volumes of several cortical regions linked to micturition control. These abnormalities were found in both patients with SCZ and normal control patients with delayed acquisition of urinary continence, although the precise anatomical structures involved differed somewhat between groups.

Startle Reflex

The startle reflex consists of a contraction of the skeletal and facial muscles in response to a sudden, relatively intense stimulus that may be represented across multiple modalities (visual, auditory, or tactile). This reflex is classified as a special subtype of a defensive response. Prepulse inhibition (PPI) of the startle response is a measure of inhibitory function and time-linked information processing, by which a weak sensory signal (the prepulse) inhibits the elicitation of the startle response caused by a sudden intense stimulus. PPI commonly is viewed as an operational measure of a process called "sensorimotor gating," by which excess or trivial stimuli are screened or gated out of awareness so the individual can focus attention on the most salient points of the stimulus-laden environment. The PPI reflects the activation of behavioral gating processes that are regulated by forebrain neural circuitry. This circuitry exerts a regulatory influence, but the signal of the prepulse need not traverse the cortico-striato-pallidopontine circuitry (ie, mediate via the forebrain circuits) to produce a PPI [26].

The startle response has been shown to be associated with deficits in the PPI response in patients with SCZ and their relatives. Aside from this group, patients with disorders in the cortico-striato-pallido-pontine circuits exhibit poor gating of motor, sensory, or cognitive information and corresponding PPI deficits. These groups include patients with obsessive-compulsive disorder, Tourette's syndrome, blepharospasm, and temporal lobe epilepsy with psychosis, enuresis, and possibly posttraumatic stress disorder. A study of startle amplitude in a subset of persons in the second and third generations in the Petersen study group [27] reported an exaggerated startle response in the high-risk group compared with the low-risk group, suggesting that exaggerated phasic arousal in these individuals in response to abrupt, startling stimuli may be linked to these right-hemisphere abnormalities [28] and may have contributed to the disturbances in attention that these participants reported. Taken together, these analyses suggest that, although cortical thinning in the right hemisphere mediates the association of familial risk for MDD with inattention and impaired visual memory, inattention mediates the

relationship between cortical thinning and the severity of MDD and anxiety symptoms most prominently when cortical thinning also is present in analogous portions of the left hemisphere. Furthermore, these findings suggest that cortical thinning of the right hemisphere in persons who are at increased familial risk for depression may produce inattention and visual memory problems even in the absence of MDD or anxiety.

Several studies have been done in pediatric urology involving PPI and startle responses. The work by Baeyens et al. [29], a 2-year follow-up study, followed up their patients with enuresis and looked for significant difference in %PPI. The authors interpreted their data as “brainstem maturation was detected in children with nocturnal enuresis, no significant effect on the current enuresis status was noted, in that children with and without enuresis at follow up did not exhibit a significant difference in %PPI increase” [29]. They felt the data demonstrated that immaturity of the brainstem, although involved in the pathogenesis of nocturnal enuresis, is not associated with its persistence. Can the assumption be wrong here, and this is not a brainstem functional problem at all, but one in which the right hemispheric function is abnormal? We can speculate this because the PPI reflects the activation of behavioral gating processes that are regulated by forebrain neural circuitry. This circuitry exerts a regulatory influence, but the signal of the prepulse need not traverse the corticostriato-pallido-pontine circuitry; it could be mediated via the forebrain circuits to produce a PPI [26]. It is possible that the assumption that the site of the problem with enuresis is in the brainstem is incorrect, and the problem actually may be a forebrain problem. Further evidence exists in the startle literature when it is combined with functional imaging studies. One of the most robust and consistent findings is that patients with anxiety show greater startle responses to safety cues, but normal startle responses to threat cues compared to control patients. In the patients with anxiety, the ACG has been implicated as a site of dysfunction, as well as the amygdala and hippocampus. Further evidence pointing away from the brainstem is the paper presented at the World Congress of Pediatric Urology in 2010 by Eggert et al. [30••], which revealed that children with enuresis had a significant decrease in PPI when they were actively engaged in a concentrated state while playing a video game. This supports a more frontal lobe-mediated problem than a brainstem dysfunction. The data fit in better with the idea of a right frontal hemispheric problem, such as seen in the patients with MDD. The startle data lend further support that the child that tells you that they had no idea that they wet themselves when actively engaged in play is actually telling the truth.

To lend more credence to these thoughts, it has become clear that the brain is always active and that doing some

form of concentrating or activity only increases brain activity minimally compared to the daydreaming state. There are centers in the brain that are constantly active regardless of the activity going on; these sites have been termed the default mode network (DMN). The areas of the brain in this network are the medial PFC, medial and lateral parietal cortices, and the lateral temporal cortex. The DMN acts as a conductor, making sure that signals from disparate areas are processed and prioritized, preventing a free-for-all of signals passing through the brain. Brain imaging studies have found altered connections among brain cells in patients with depression, autism, SCZ, and Alzheimer’s disease [31]. These alterations can lead to poor coordination of processing and to incontinence either when playing or in cases of giggle incontinence. We have found that imipramine, norepinephrine reuptake inhibitors, and selective serotonin reuptake inhibitors are most effective for giggle incontinence. They may be helping with modulation at this site or in the network.

Another network that has been identified, and again it is in the PFC, is BA 25 (also known as area 25), which is a hub for the depression circuitry. This area is extremely rich in serotonin transporters. A study looking at individuals with short and long variations of the transporter gene found that patients with the short gene variant had a higher rate of depression, but more importantly, they had cortical thinning in this area. It was found that BA 25 was uncoupled from the subcortical brain regions like the amygdala and insula, which affect anxiety and mood; the hypothalamus and brainstem, which influence changes in sleep, appetite, and energy; the hippocampus, which affects memory processing and attention; and parts of the frontal cortex that affect insight and self esteem [32].

There are robust data from neuroimaging, startle reflexes, and lineage studies to implicate the areas in the frontal lobes, and in particular, the PFC and ACG, with many of the problems associated with LUTS and incontinence.

How Does This Correlate to Children?

We now understand that there is a link between adult neuropsychiatric disorders that affect the right frontal cortex and voiding dysfunction. The traditional psychoanalytic view of depression in children, that their superegos were not sufficiently developed, has been disregarded in the past 10–20 years. There is growing evidence that children as young as 2 years can have depression [33], which, as we have seen, is associated with right frontal lobe dysfunction and cortical abnormalities. The present-day feeling is that chronic mental illness is a disease of the young. These problems begin when we are young and shape us into the adults that we become. If depression can be present, can

other neuropsychiatric problems also may be present at this age, or even at a younger age? There is evidence from the long-term longitudinal follow-up of patients with what was initially described as inhibited and uninhibited temperament that children with an inhibited temperament tend to avoid people and objects that are novel or unfamiliar [34]. Uninhibited children approach novel persons or objects readily. It has been shown that an inhibited temperament is a risk factor for the development of anxiety in both childhood and adolescence, and in particular, social phobia. The amygdala has been implicated as a major player in these patients with inhibited temperament and they tend to be high reactors. The amygdala becomes activated even to novel nonthreatening faces in experimental studies. This occurs because the amygdala participates in states of vigilance as well as fear [34]. The authors suggest, “The amygdala is specialized for the detection, processing and integration of stimuli that have potential biological import, of which threat is only one possible example” [34]. Because it is known that situations that are stressful for individuals will lead to the development of bypass mechanisms that lead straight to the amygdala and do not lead to the areas involved in executive decision making (PFC and ACG), one can see where some childhood situations can lead to abnormal or elevated responses by the amygdala and can see the ensuing cascade of problems that can occur from this.

These temperament changes can be seen as early as 4 months, and many of these patients will outgrow their fearfulness. Children have been classified as inhibited (high reactive) or uninhibited (low reactive), and the inhibited ones are the ones that are more likely to go on and develop social anxiety disorders. It was found that by age 15 years, two thirds of those who had been high reactors in infancy behaved pretty much like everybody else [3]. Work has been done showing that the PFC in high-reactive individuals increases in size. It is unclear if this is a mechanism for compensating for the overactivity of the amygdala in these patients and if it allows them to suppress their fears. Taking things one step further, they separated the high reactors from those that did and did not have social anxiety, and they found that the ones that had social anxiety had significant cortical thinning. This confirms other findings of cortical thinning in the PFC in patients with anxiety.

The aforementioned findings have potential implications in the children that we see with incontinence. It gives us the ability to postulate why children seem to outgrow their urge incontinence and urgency problems. In these high-reactive patients, our treatments have allowed us to temporize and buy time so that, eventually, the brain has a chance to change and fix the problem. In some cases, the PFC does not compensate and we are left with those patients that become adults with urgency and frequency. These findings

parallel the findings of Stone et al. [35•], where up to one third of their patients did not get better by age 18 years. If the amygdala responses are left unchecked by a thinned PFC, these amygdala responses due to their multiple innervation pathways to other areas of the brain, especially the hypothalamus, can lead to unwanted effects downstream in the spine and bladder.

A stressful situation in a bathroom, fear of going to the bathroom in a strange place because the mother has drilled it into their head that they shouldn't use outside toilets, or fear of having a painful bowel movement because the last one was painful all can lead to exaggerated amygdala responses, which in turn can lead to elevated norepinephrine levels, which can be associated with problems in opening of the bladder neck and possibly straining to void and the development of inappropriate pelvic floor activation. Prolonged exposure or repetitions of these scenarios can lead to permanent changes due to abnormal behavior, elevated NE levels, or increased secretion of corticotrophin-releasing factor. These effects can lead to the further physiologic changes in receptors, and even in the muscle and blood vessels, of the bladder. These changes can lead to alterations in expression of neurotransmitters and other inflammatory agents, which could potentially lead to diseases such as OAB and interstitial cystitis.

Conclusions

The literature is full of articles that preach the bladder as the center of all evils when it comes to voiding problems [36]. From the data presented here, it appears that there is a strong case to be made to implicate the brain as the primary site for most LUTS in adults and children in particular. It seems evident from the data that these problems can be present as early as several months, and there is no reason to believe that they are not present at birth or even in utero.

If we adhere to the idea that we should be able to use one disease to explain the comorbid findings in patients with OAB (either adult or pediatric), it is clear that using a neurocentric model is much more likely to explain the association between encopresis, obesity, depression, and urinary incontinence than to try to explain it as four separate diseases. Identification of the single disease site would facilitate treatment and prevent frustration on the patient's side.

In this case, the ability to verify our suspicions, especially in children, is limited by ethical and technical limitations with neuroimaging and testing. Further confounding things is the fact that the present establishment is heavily invested in pharmacological treatment of the bladder and that it would be very difficult to garner the support to prove the neurocentric theory within the

urological circles. We can see a possible corollary with Einstein's theory of relativity and the bending of light by gravity. This phenomenon was predicted by his theory, but it took many years after its publication for scientists to show the actual phenomenon exists. We may see a similar occurrence, given enough time and enough literature in the respective fields of the comorbid diseases, that eventually the disparate findings will be put together, and what is purely conjecture at this time will be proven.

Disclosures Dr. Israel Franco serves as a consultant for Sanofi, Novartis and Allergan, and has previously served as a consultant for Astellas Pharma and LABORIE.

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