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Original Article

Delirium in patients with dementia and in children: Overlap of symptoms profile and possible role for future diagnosis

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ABSTRACT

Background: Delirium in the extremes of the age spectrum may show similarities in presentations, and these similarities may provide information to develop tools for the diagnosis of delirium superimposed on dementia (DSD). We sought to investigate the symptom profile and subtypes of delirium in patients with dementia, and in infants and preschool children.

Methods: This was an exploratory analysis of previous prospective cohort studies that evaluated delirium with the DSM-IV criteria in patients with dementia, and in critically ill infants (< 2 years of age) and preschool children (2–5 years of age), respectively. Delirium subtypes were defined based on the Richmond Agitation-Sedation Scale.

Results: We included 147 patients, 35 adult patients with delirium DSD, 80 infants, and 32 preschool children with delirium. Hypokinesia and apathy were common among both DSD (72%), infants (74%) and preschool children (75%) with delirium, whereas hallucinations and anxiety were less common in both adults with DSD (26%) and infants (10%) and preschool children (14%). Hypoactive delirium was most common delirium subtype among infants (68%) and preschoolers (76%), whereas RASS = 0 (alert) delirium was the most common among adult patients with DSD (55%).

Conclusions: The study reports similarities in the symptoms profile of delirium in a cohort of patients with dementia and delirium, and in infants and preschool-aged children with delirium. These preliminary findings might be informative to design future studies adapting delirium assessments used in in infants and preschool-aged children to patients with dementia, especially in the moderate to severe stages.

1. Introduction

Delirium is an acute neuropsychiatric disorder characterized by inattention and a disturbance in awareness and cognition that develops over a short period of time, and cannot be explained by a pre-existing cognitive impairment [1]. There is evidence that the disturbance is caused by the direct consequences of a medical condition or medications and reported prevalence rates range from 10 to 80% depending on the population studied [2]. Though it is now well recognized that the occurrence of delirium is associated with adverse outcomes, it is still often under recognized and poorly documented [2,3].

Dementia is defined according to the DSM-IV criteria as a

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progressive development of memory impairment along with other cognitive deficits including aphasia, apraxia, agnosia and disturbance in executive functioning with a significant impairment in social and occupational functioning. These changes represent a significant decline from a previous level of functioning.

The diagnosis of delirium superimposed on dementia is a challenge due to difficulties in ascertaining when the cognitive changes are related to the dementia or to an acute change as in the context of delirium [4]. The evaluation of delirium in the context of dementia requires a different approach than delirium without dementia. Indeed, it is still uncertain which tools should be used to assess inattention and unawareness - the cardinal features of delirium- in this specific population, since many of the usual tests for inattention (months of the year backwards, days of the week backwards, the serial 7's etc.) require a certain level of arousal and awareness that may be diminished in patients with dementia. Previous studies have reported the use of the abovementioned test for inattention but without specifying the performances of these tests in the presence of dementia and which test could have better performances in the population for dementia. For instance the digit span, the months of the year backwards, and the days of the week backwards are most often used for delirium evaluation [5].

Researchers have tried to investigate the level of arousal as a proxy measure for inattention, especially in the context of dementia [6–8]. Other investigations have also evaluated if motor fluctuations could be useful in identifying delirium especially in the more advanced stages of dementia [9]. To date there are no specific tools designed to assess the presence of delirium superimposed on dementia (DSD) and there are uncertainties on how the DSM-5 criteria should be used and adapted to these populations [10,11]. Despite these challenges, the prevalence of delirium superimposed on dementia (DSD) in community and hospital populations has been reported between 22% to 89% [12]. There is also a strong relationship between delirium and dementia, with an increased risk of delirium with greater severity of dementia [13].

Among pediatric patients, delirium prevalence has been reported between 10 and 49% in critically ill and cancer patients [14–18], with rates of 56% in critically ill infants and toddlers [17]. The Pediatric Confusion Assessment Method for the ICU (pCAM-ICU), the PreSchool Confusion Assessment Method for the ICU (psCAM-ICU), and the Cornell Assessment for Pediatric Delirium (CAPD) now provide valid and reliable tools for assessing delirium in children as young as 6 months of age and utilize both objective and subjective criteria [15–17].

The value of observational evaluations is high when assessing for conditions such as pain among adult patients with dementia and in pediatric patients, taking into account obstacles to communication from cognitive impairment or natural development. In fact, the American Geriatric Society encourages the incorporation of 6 behavioral domains (i.e., facial expressions, verbalizations/ vocalizations, body movements, changes in interpersonal interactions, changes in activity patterns/ routines and mental status changes) when conducting pain assessments among seniors with dementia. Interestingly, a recent investigation reported similarities in the symptoms profile of delirium in older adults and children in particular regarding the presence of sleep-wake cycle disturbances, language and motor alterations [19]. Given the possible existing similarities between patients with dementia and children we sought to further investigate the symptom profile and subtypes of delirium in a multicenter study including patients with dementia, infants and preschool children.

2. Methods

This was a multicenter secondary analysis of two previous prospective cohort studies that evaluated delirium in patients with dementia, and in critically ill infants and preschool children (< 5 years of age). The local institutional review board or appropriate ethics committee in each institution reviewed and approved this study. Of these cohorts we selected all patients who had at least one episode of delirium as described below.

2.1. Evaluation of the DSD cohort

This cohort has been previously described in details [20,21]. Two expert geriatricians diagnosed patients' delirium according to the Diagnostic and Statistical Manual of Mental Disorders (4th edition, text revision) (DSM-IV-TR) criteria with a standardized approach previously described [22]. The motor subtype of delirium (i.e., hypoactive, hyperactive, mixed, non hyperactive-hypoactive) was defined using the modified-Richmond Agitation and Sedation Scale (m-RASS) [23]. The phenomenology of delirium was evaluated using the Delirium-O-Meter (D-O-M) [24], a nurses' rating scale for monitoring delirium severity in geriatric patients. The D-O-M includes twelve symptoms of delirium: sustained inattention; shifting attention; orientation; consciousness disturbance; apathy; hypokinesia/psychomotor retardation; incoherence; fluctuation functioning (diurnal variation/sleep wake cycle); restlessness (psychomotor agitation); delusions; hallucinations; and anxiety/fear. The total score ranges from 0 (absence of symptoms) to 36 (severe symptoms).

The presence and type of dementia (i.e., Vascular Dementia, Alzheimer Dementia, Lewy Body Dementia, Other) was ascertained by reviewing patients' medical records. Additionally, two expert neuropsychologists confirmed and rated the severity of dementia interviewing the caregivers at the time of enrollment with the Clinical Dementia Rating (CDR) Scale [25] and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), with a cut-off of 3.3 indicative of cognitive impairment [26]. The CDR score ranges from 1 to 3: 1 (mild dementia); 2 (moderate dementia); 3 (severe dementia).

2.2. Evaluation of the pediatric cohort

A prospective observational cohort of pediatric patients, aged 6 months to 5 years admitted to the pediatric ICU at Monroe Carell Jr. Children's Hospital at Vanderbilt (MCJCHV) regardless of diagnosis were enrolled for validation of the psCAM-ICU and to determine associated risk factors and outcomes for delirium. The reliability and validity of the psCAM-ICU in infants and young children, as well as associated risk factors and outcomes, has been published [17]. In this cohort, patients were assessed daily for delirium using the psCAM-ICU for up to 14 days or until transfer/discharge from the PICU, whichever came first. The psychiatry team used the recently published Vanderbilt Assessment for Delirium in Infants and Children (VADIC) [27], based on DSM-criterion for delirium, as a framework for patient assessments and included the following features: 1) acute change or fluctuation in mental status, 2) attention (focus, sustain, or shifting attention), 3) alteration in level of consciousness, 4) alterations in perception (hallucinations, hyperacusis), 5) cognition & orientation, 6) sleep wake cycle disturbance, 7) changes in affect; 8) language and thought Incoherence was denoted as normal, mild, moderate, or severe based on parts of the language and thought assessment of the VADIC. The approach to patient assessment using the VADIC recognizes the importance of family involvement and the need for reassurance that many pediatric patients require. The examiner is encouraged to utilize the bedside caregivers to engage with the child for required tasks through play and compare the child's reaction in the moment to the previously established baseline expectation. Serial documentation of the pattern in patient responses to these objective assessments facilitates the tracking of the course of attention and cognition. Determination of hypoactive, hyperactive, and mixed subtypes were made using the Richmond Agitation-Sedation Scale (RASS) by the reference standard.

2.3. Describing patterns of phenomenology

Most of the symptoms or features assessed using the DOM and VADIC were similar and easily compared to one another. Incoherence,

apathy, hypokinesia, and anxiety/fear from the DOM assessment were compared to key parts of the eight features assessed with the VADIC. Incoherence in infants and children was determined using portions of the language and thought feature assessment. Apathy was assessed using portions of the attention, affect, and language/thought features, including spontaneity, social smile, and reaction to peek-a-boo as examples. Hypokinesia was determined using portions of the arousal assessment imbedded in the VADIC tool. Anxiety/fear were determined as part of the affect and level of consciousness VADIC assessment.

2.4. Statistical analysis

Patient characteristics were summarized using descriptive statistics including median, interquartile range, and percentages. We describe the prevalence of delirium symptoms among geriatric patients with DSD and delirious pediatric patients (divided into infants and preschoolers) as determined by the reference rater child psychiatrists using the VADIC tool. Geriatric patients with dementia (CDR ≥ 1) and at least one delirium assessment and pediatric patients with at least one instance of confirmed delirium as assessed by the psychiatric reference rater was included in this analysis. We examined the prevalence of 12 specific symptoms of delirium among adults with DSD and pediatric delirium among infants and younger children including: 1) attention, 2) orientation, 3) consciousness, 4) apathy, 5) hypokinesia, 6) incoherence, 7) fluctuation in functioning (sleep-wake cycle disturbances), 8) restlessness, 9) delusions, 10) hallucination, 11) anxiety, and 12) inconsolability. The prevalence of each delirium symptom was also analyzed among patients with hypoactive versus hyperactive delirium. Delirium subtypes were defined by the RASS in adults with DSD and pediatric patients (RASS < 0 = hypoactive; RASS > 0 = hyperactive, and RASS = 0 non-hyperactive, non-hypoactive).

3. Results

One-hundred forty-seven patients with delirium were included in this cohort; 35 adult patients with delirium superimposed on dementia (DSD), 41 preschool-aged children (age 2–5 years), and 92 infants (6 months-5 years) (Table 1). Of the included adult patients with DSD, 43% (n = 15) were classified as having mild dementia, 37% (n = 13) moderate dementia, and 20% (7) severe dementia. The most frequent type of dementia was Alzheimer Dementia (49%; n = 17) followed by Vascular dementia (26%; n = 9), Lewy Body dementia (35%; n = 3), and other types of dementia (35%; n = 3). Among the pediatric cohort, the most common admission diagnosis for both infants (39%) and preschool-aged children (24%) to the PICU was acute respiratory distress syndrome (ARDS).

Delirium was diagnosed in 102 adult DSD assessments, 178 infant assessments, and 57 preschooler assessments. The prevalence of twelve specific delirium symptoms were compared between adults with DSD, preschoolers and infants (Table 2, Fig. 1). Among the twelve symptoms of delirium, almost all patients demonstrated the presence of both inattention and fluctuation in functioning (sleep-wake cycle disturbances). Hypokinesia and apathy were commonly assessed for and present among both adults with DSD and pediatric patients with delirium. Whereas, hallucinations and anxiety were less commonly assessed nor observed in both adults with DSD and pediatric patients. Incoherence was most prevalent in DSD patients compared to the pediatric population.

Table 1
Characteristics of patients in the delirium superimposed on dementia (DSD), infants and preschool children cohorts.

Variable	Adult, DSD (N = 35)	Infant (N = 92)	Preschool (N = 41)
Age (years/months)	85 (82–89)	10.5 (7–16)	36 (28–36)
CDR 1	15 (43%)	–	–
CDR 2	13 (37%)	–	–
CDR 3	7 (20%)	–	–
IQCODE	4.3 (3.9–4.8)	–	–
PRISM SCORE	–	6 (0 – 12)	6.5 (5–14)
Length of ICU stay		8.5 (3, 21)	10 (4–24)
Discharged alive	35 (100%)	91 (99)	41 (100)

Clinical Dementia Rating Scale (CDR); Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE); DSD, delirium superimposed on dementia.

Table 2
Prevalence of 12 symptoms of delirium in the DSD, infants and preschool children cohorts. The table shows the prevalence for each symptom in each population, as number of assessments with a specific symptom (percentage of all delirious assessments; percentage of all delirious assessments where this symptom was evaluated). Two percentages are sometimes required because not all symptoms could be evaluated at all assessments, especially in the pediatric population.

Variable	Adult, DSD (N = 102)	Infant (N = 178)	Preschool (N = 57)
Inattention	102 (100%)	158 (89%)	52 (91%)
Disorientation	101 (99%)	52 (29%)	31 (54%)
Consciousness disturbance	63 (62%)	163 (92%)	50 (88%)
Apathy	79 (77%)	153 (86%)	50 (88%)
Hypokinesia	73 (72%)	132 (74%)	43 (75%)
Incoherence	98 (96%)	27 (15%)	25 (44%)
Fluctuation functioning	85 (83%)	178 (100%)	56 (98%)
Restlessness	43 (42%)	36 (20%)	8 (14%)
Delusions	43 (42%)	Not applicable	Not applicable
Hallucination	27 (26%)	18 (10%)	8 (14%)
Anxiety	50 (49%)	62 (35%)	19 (33%)
Inconsolability	Not applicable	41 (23%)	7 (12%)

The prevalence of delirium subtypes was determined by the Richmond Agitation-Sedation Scale (RASS) score, when present. Hypoactive delirium (RASS < 0) was most common among infants (68%) and preschoolers (76%), whereas RASS = 0 delirium was the most common among adult patients with DSD (55%) (Table 3). Hyperactive delirium (RASS < 0) was the least common among adults with DSD, whereas, RASS = 0 delirium was the least common among infants and preschoolers. The prevalence of delirium symptoms among patients with hypoactive delirium were compared. Among the twelve symptoms of delirium, almost all patients demonstrated the presence of inattention, acute alteration of consciousness, apathy, hypokinesia, and fluctuation in functioning (sleep-wake cycle disturbances). (Fig. 2) Hallucinations and anxiety were again inconsistently evaluated and observed in both adults with DSD and pediatric patients. As there were so few adult patients with hyperactive delirium and few pediatric patients with RASS = 0 delirium, description of symptom prevalence was not informative.

4. Discussion

To our knowledge this is the first study to specifically describe the symptoms profile of delirium in a cohort of patients with dementia and delirium, and in infants and preschool-aged children with delirium. We found similarities in the frequency of both the assessment and presence of inattention, hypokinesia, fluctuation in functioning (sleep-wake cycle disturbances), and apathy across the three cohorts. Among those patients with hypoactive delirium, altered level of consciousness was also commonly observed. It was interesting that the RASS = 0 delirium subtype was most common among adults with DSD versus the hypoactive or mixed delirium subtypes that are commonly reported as the most frequent among both adult and pediatric patients.

Delirium phenomenology and the variations in delirium manifestations between pediatric and adult patients have been previously investigated in few studies [19,28] but no studies has specifically compared the symptoms profile of delirium among the youngest of pediatric

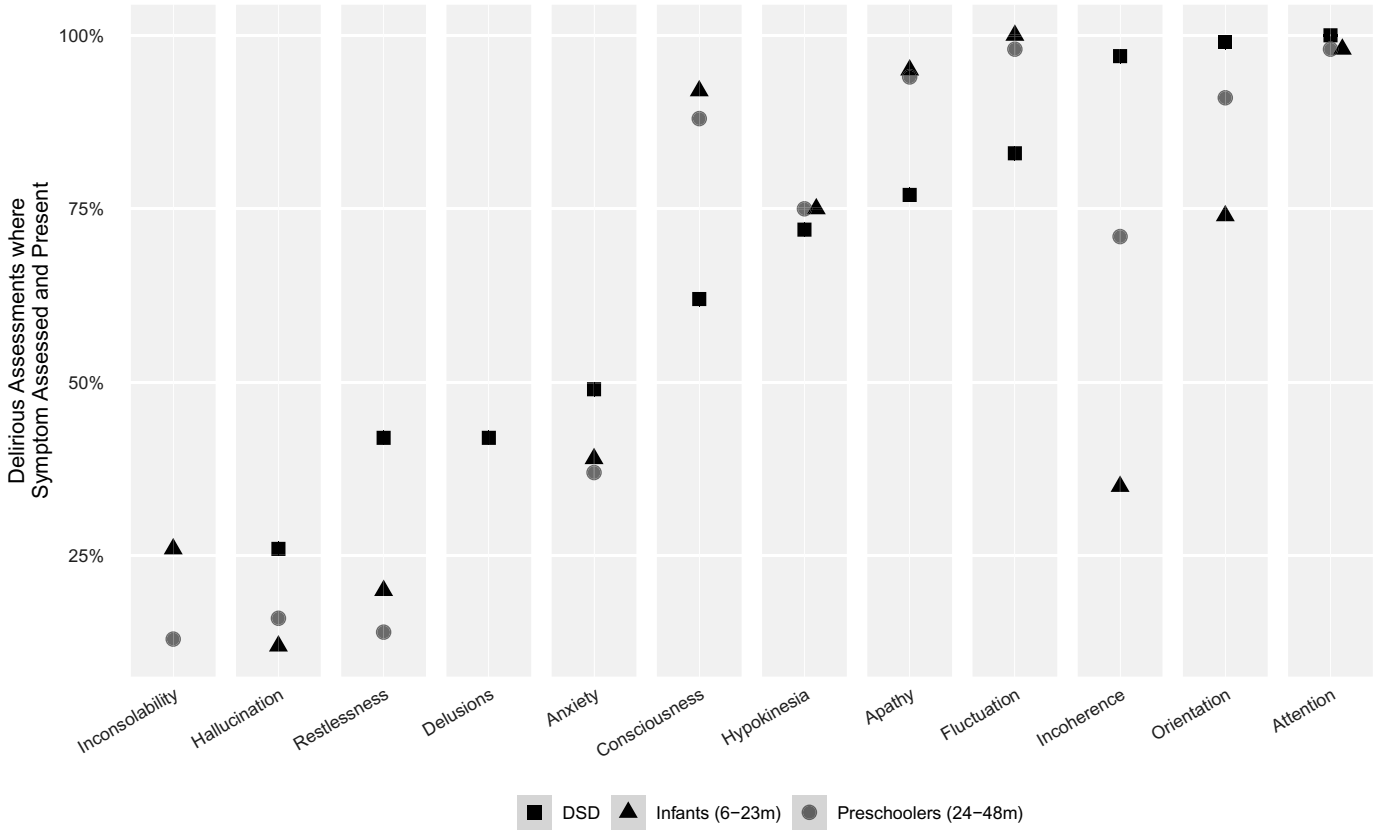

Fig. 1. Symptoms of delirium in dementia patients, infant and preschool children.

Table 3
Distribution of delirium subtypes in dementia patients, infant and preschool children.

Delirium subtype	Adults, DSD	Infants	Preschoolers
	N = 100	*N* = 91	*N* = 25
Hypoactive	32 (32)	62 (68)	19 (76)
Hyperactive	13(13)	24 (26)	2 (8)
Non hyper - non hypoactive (RASS = 0)	55 (55)	5 (5)	4 (16)

DSD, Delirium superimposed on dementia.

patients and adult patients with dementia. Grover and colleagues have compared delirium in children and adolescents (age 8–18 years) with adults and geriatric patients, reporting similar phenomenology of delirium [19]. Compared to adults, however, children and adolescents had lower frequency of long-term memory and visuospatial disturbances. Contrarily, children and adolescents had higher frequency of lability of affect than the elderly. A previous investigation reported a different delirium profile in children compared to adults and geriatric patients [28]. Delirium in children was characterized by a more acute onset, more severe perceptual disturbances, more frequent visual hallucinations, more severe delusions, more severe lability of mood, greater agitation, less severe cognitive deficits, less severe sleep-wake cycle disturbance, and less variability of symptoms over time. Similarly, Turkel et al. showed a higher frequency of sleep-wake disturbance, fluctuating symptoms, impaired attention, irritability, agitation, affective lability, and confusion in children. Conversely, impaired memory, depressed mood, speech disturbance, delusions, and paranoia, were more often present in adults [29]. In our investigation we found a high prevalence and a similarity of the fluctuation in functioning (sleep-wake cycle disturbances) and hypokinesia in the three cohorts compared to the above-mentioned studies. This is indeed interesting given the previously published literature investigating the role of changes in the level of arousals and motor fluctuations in identifying delirium especially in the more advanced stages of dementia [6–8, 9]. Tieges and colleagues assessed patients with delirium using a new tool (the Observational Scale of Level of Arousal OSLA) [6], for delirium by observing eye opening, eye contact, as well as patient posture and movement. Similarly, the pediatrics tools are less oriented on the use of formal cognitive testing and includes more observations of children behaviours. Additionally, delirium is not an isolated mental disorder, but affects motor function as well [30,31]. The evaluation of posture and movement might indeed be of interest in the context of patients with dementia. A study comparing 4 groups of 15 patients (with delirium alone, with dementia alone, with delirium superimposed on dementia and with neither delirium nor dementia) found that when delirium develops, a worsening of motor performance also occurs specifically in patients with dementia [31]. Finally, a more recent study described how changes in the level of arousals are highly specific for delirium in a large population of patients with dementia admitted to different settings [32].

The lessons learned from the adaptations of delirium assessment tasks in pediatric patients have been informative to the ability to separate attention and cognitive assessments. Key in a population that demonstrates such a vast range of cognitive and language capabilities. The limitations of DSM-5 criterion not addressing these variations in development that can be observed among pediatric and adults with dementia may be considered a disadvantage to core criterion. However, a recent study has highlighted these unique variations in development, cognition, and environmental factors to possibly facilitate the development of the most efficient and accurate delirium tools in clinical practice [33]. While our study demonstrates some similarities in delirium symptoms among adults with DSD and infants and preschool-aged children with delirium, the message may remain in the importance of the type of assessment. DSM-5 criteria specifically focus on the

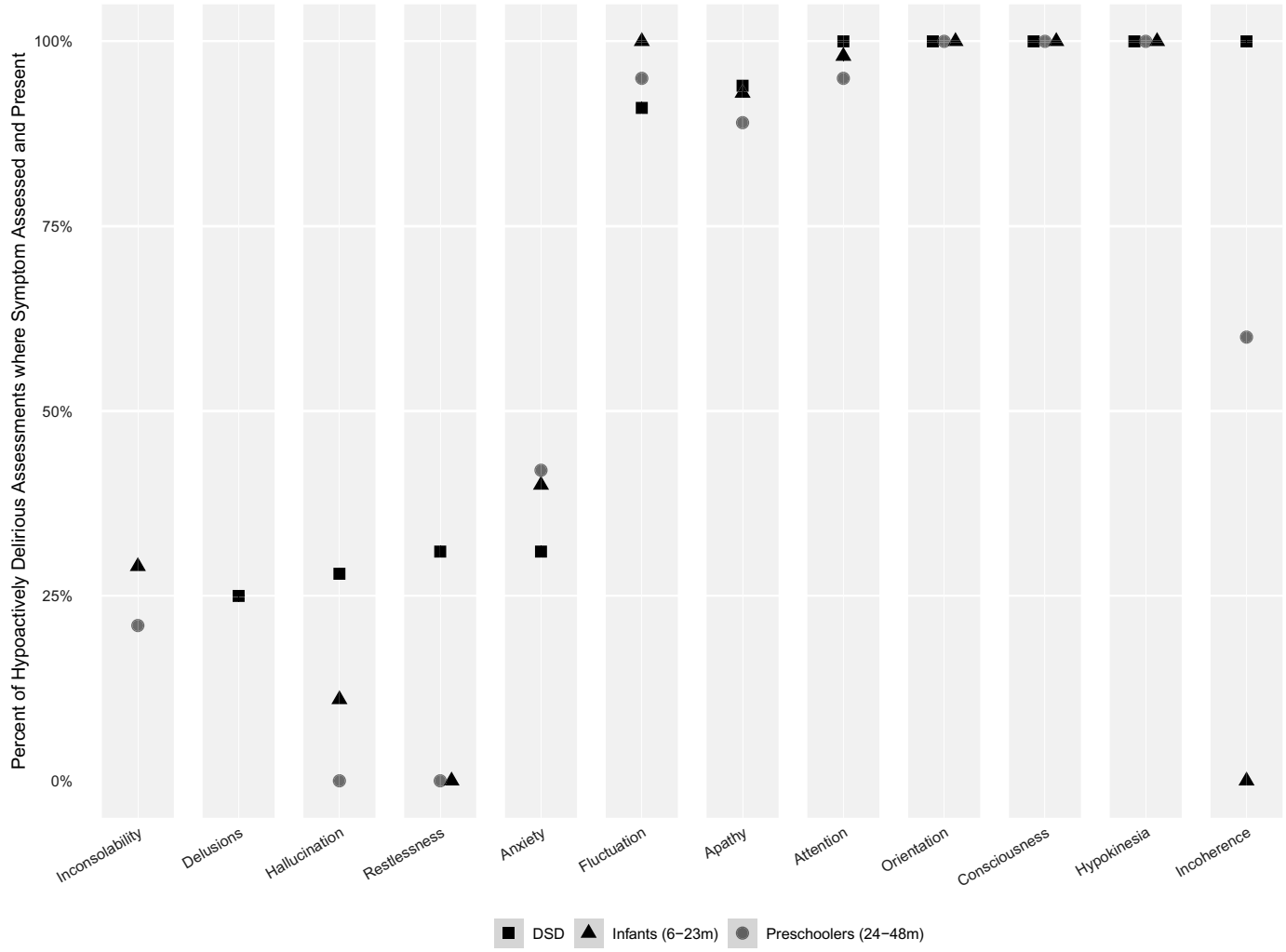

Fig. 2. Symptoms of delirium in dementia patients, infant and preschool children with hypoactive delirium.

importance of determining a "change in cognition not better explained by a pre-existing, established or evolving neurocognitive disorder," such as dementia. In order to determine this, delirium tools will have to embrace the unique assessments required for inattention and cognition in these complex populations. In this challenging population, especially in the advanced stages of dementia, assessments tasks used in infants and preschoolers might help differentiating delirium from dementia. Another important point is the presence of inattention, which is expected being inattention a cardinal feature of delirium according to the DSM-5 definition. Given the presence of similarities in other delirium symptoms it use useful to understand what tests were used to test the presence of inattention in the studied population. In the population of older patient with dementia Attention was evaluated using several first, the patient was asked to state the days of the week forward and backwards, and to count backwards from 20 to 1. Any error in each of these tasks was considered as inattention. An additional test was the SAVE-AHAART vigilance task embedded in the Confusion Assessment Method — ICU (CAM-ICU) [34]. In the pediatric cohort, children were tested for inattention using the VADIC evaluation [27]. In the VADIC evaluation the psychiatrists did not use a formal test for inattention but attentional disturbances are tested evaluating the interaction of the child with the environment. For instance Gangopadhyay describes an illustration of "having the parent walk from one side of the bed to the other and observe how the child focuses and sustains attention with the parent through this movement and comparing reactions in that circumstance to the evaluator (relatively unknown to the child) performing the same task [27]. The evaluator asks the parent if the reactions are baseline behavior or not in each interaction, and if not, the parent describes the differences observed." [27] This type of evaluation might indeed be useful in the advanced stages of dementia. For instance one might think about testing the patient on the interaction with a series of simple cards or mirrors as indicated in the psCAM-ICU [17]. The psCAM-ICU was specifically adapted from the pediatric and adult CAM-ICU to address the neurocognitive variations expected in the natural development of childhood and also the regression of skills observed during critical illness [15,17,34]. Most obvious are the immature language and cognitive skills of the very young (infants and preschoolers). Hence, the psCAM-ICU adopts unique evaluations for inattention and dysregulated systems (i.e. disorganized thinking) using specific tasks. In details, inattention is evaluated by showing five colorful and elementary pictures and five reflective mirrors allowing the infant/child to view themselves (ten total cards, ~ 10 s of expected attention). The accessor then observes how many cards the infant/child looks at (eye contact) and can further record how a child interacts with the picture (reaching out, making faces, tracking). Therefore, the evaluation for inattention specifically avoids the need for advanced cognitive or language skills which this unique patient population has yet to develop. Similar to our DSD population, which experience loss of cognitive, or language skills they once possessed. Therefore, future studies are required to evaluate how behavioral observations might indeed be more useful to test attention in patients with advanced dementia instead of using formal tests of inattention.

The assessment of disorganized thought, found in the adult and pediatric CAM-ICU, also required adaptation to address the not yet fully developed neurocognitive skills of infants and younger children. Obviously, infants would be unable to answer yes/no questions or be expected to perform a command. The psCAM-ICU assesses for dysregulated systems which is indirectly assessing processes required for organized thought in older patients with more developed neurocognition. Observational components including the presence of inconsolability, unawareness of surroundings, and sleep-wake cycle disturbances were included. Of those, the presence of a sleep wake cycle disturbance provided the greatest specificity and sensitivity in further delineating the presence of delirium in infants and younger children who already demonstrated having an acute change or fluctuation from baseline mental status and were inattentive [17]. Finally, the lower prevalence of incoherence in the infants compared to younger children and DSD patients deserves a brief explanation. The assessment and diagnosis of incoherence is tied largely to language. In the setting of limited language development, as it is in the infants, we are unable to fully determine its presence. Hence why as children age and development of language progresses, incoherence becomes a more prominent symptom of delirium when present.

Future studies should further investigate how these innovative assessments might indeed increase our ability to detect delirium superimposed in dementia patients. In particular, separating the important assessment of attention from the assessment of cognition. Many current tests for inattention in adults are based on some lower level of expected understanding or communication skills, which may be declining in our DSD population. The goal becomes assuring that our techniques of evaluation for delirium are not simply re-assessing cognitive impairment which is present at baseline given the dementia.

The study has strengths along with limitations. This is the first study to specifically report symptoms of delirium in patients with dementia and in critically ill infants and preschool children (< 5 years of age), using a structured delirium assessment. However, we were unable to compare delirium severity across the 3 cohorts and thus to provide information on possible differences on delirium phenomenology. Additionally, we have not included a subgroup of older patients without dementia in this preliminary investigation. Future, larger investigations should compare the delirium symptoms' profile also in the population without dementia to clarify if the symptoms described in this manuscript are indeed dementia specific.

5. Conclusions

In this study we found similarities in the symptoms profile of delirium in a cohort of patients with dementia and delirium, and in infants and preschool-aged children with delirium. These preliminary findings might be informative to design future studies adapting delirium assessments used in in infants and preschool-aged children to patients with dementia, especially in the moderate to severe stages.

Conflict of interest declaration

None

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Appendix A. Suplementary data

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