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Cognitive behavioral therapy in 22q11.2 microdeletion with psychotic symptoms: What do we learn from schizophrenia?

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ABSTRACT

The 22q11.2 deletion syndrome (22q11.2DS) is one of the most common microdeletion syndromes, with a widely underestimated prevalence between 1 per 2000 and 1 per 6000. Since childhood, patients with 22q11.2DS are described as having difficulties to initiate and maintain peer relationships. This lack of social skills has been linked to attention deficits/hyperactivity disorder, anxiety and depression. A high incidence of psychosis and positive symptoms is observed in patients with 22q11.2DS and remains correlated with poor social functioning, anxiety and depressive symptoms. Because 22q11.2DS and schizophrenia share several major clinical features, 22q11.2DS is sometimes considered as a genetic model for schizophrenia. Surprisingly, almost no study suggests the use of cognitive and behavioral therapy (CBT) in this indication.

We reviewed what should be learned from schizophrenia to develop specific intervention for 22q11.2DS. In our opinion, the first step of CBT approach in 22q11.2DS with psychotic symptoms is to identify precisely which tools can be used among the already available ones. Cognitive behavioral therapy (CBT) targets integrated disorders, i.e. reasoning biases and behavior disorders. In 22q11.2DS, CBT-targeted behavior disorders may take the form of social avoidance and withdrawal or, in the contrary, a more unusual disinhibition and aggressiveness. In our experience, other negative symptoms observed in 22q11.2DS, such as motivation deficit or anhedonia, may also be reduced by CBT. Controlled trials have been studying the benefits of CBT in schizophrenia and several meta-analyses proved its effectiveness. Therefore, it is legitimate to propose this tool in 22q11.2DS, considering symptoms similarities. Overall, CBT is the most effective psychosocial intervention on psychotic symptoms and remains a relevant complement to pharmacological treatments such as antipsychotics.

1. Introduction

Numerous studies have characterized the cognitive and psychiatric phenotype associated with 22q11.2 microdeletion. The 22q11.2 deletion syndrome (22q11.2DS) is one of the most common microdeletion syndromes, with a widely underestimated prevalence between 1 per 2000 and 1 per 6000 (Shprintzen, 2008), which is associated with a broad physical phenotypic spectrum, heart disease, velopharyngeal dysfunctions, thymic aplasia especially congenital, hypoparathyroidism/hypocalcemia and facial dysmorphology. 22q11.2DS is also associated with a psychiatric phenotype that includes deteriorated socio-emotional behavior, generally characterized by withdrawal, shyness, mood disorders, and difficulties in the expression of emotions (Jansen et al., 2007).

Since childhood, patients with 22q11.2DS are described as having difficulties to initiate and maintain peer relationships. This lack of social skills has been linked to attention deficits/hyperactivity disorder (ADHD), anxiety and depression (Jolin et al., 2012; Shashi et al., 2012). A high incidence of psychosis and positive symptoms is observed in patients with 22q11.2DS (Jalbrzikowski et al., 2012), and remains correlated with poor social functioning (Baker and Skuse, 2005) and anxious and depressive symptoms (Table 1). Negative symptoms are also frequent in 22q11.2DS with

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Table 1
Psychiatric symptoms in schizophrenia and 22q11.2DS Main references: Flaum and Andreasen, 1991; Mazumder et al., 2015; Stoddard et al., 2010.

Symptoms	Frequencies in schizophrenia	Frequencies in 22q11DS	Main characteristics
Hallucinations – perceptual abnormalities	35–50%	21–32%	Auditory-verbal hallucinations in second and third persons are the more specific symptoms of schizophrenia. In 22q11, hallucinations, mostly auditory and less frequently visual, can be expressed in the simple form of illusions
Delusions	64–89%	10%	Delusions can be determined by hallucinations and/or cognitive biais (e.g. jump to conclusions)
Disorganization (conceptual, behavioral)	37%	6-55%	Disorganization was seen as the underlying mechanism of the entire schizophrenic problematic. It covers a very heterogeneous set of events
Suspiciousness-persecution	54%	5–10%	The most common delusional themes, determined by hallucinations
Grandiosity	24%	7–10%	(in schizophrenia and 22q11DS) and delusions of influence (in schizophrenia)
Excitement	47%	–	Mood disorders are frequently associated to schizophrenia
Blunted affect-affective flattening	55–89%	35–49%	Negative symptoms are frequent (without specificity) and strongly
Emotional withdrawal	56%	25%	linked to functional outcomes
Social withdrawal	44%	32%	
Lack of judgement and insight	87%	–	Very frequent in schizophrenia and in 22q11 (without specificity) and strongly linked to functional outcomes
Poor attention-cognitive troubles	81%	44–50%	Very frequent (without specificity) and strongly linked to functional outcomes
Uncooperativeness	45%	–	Favored by persecution

-: data unavailable.

more than 80% of teenage or young patients showing at least one symptom with moderate to severe intensity (Stoddard et al., 2010). These symptoms are good predictors of adaptive abilities. Accordingly, 22q11.2DS is one of the most frequent known genetic risk factors for schizophrenia (Karayiorgou et al., 2010), accounting for up to 1–2% of cases in the general population and with approximately 30% of patients developing schizophrenia in adolescence or early adulthood (Monks et al., 2014). Because 22q11.2DS and schizophrenia share several major clinical features, 22q11.2DS is sometimes considered as a genetic model for schizophrenia. Surprisingly, almost no study suggests the use of cognitive and behavioral therapy (CBT) in this indication.

Considering all these data, we reviewed what should be learned from schizophrenia to develop specific intervention for 22q11.2DS. In our opinion, the first step of CBT approach in 22q11.2DS with psychotic symptoms is to identify precisely which tools can be used among the already available ones.

2. Cognitive behavioral therapy: main principles

Behavior therapy was first develop to treat phobia in the 1920s by progressively exposing patients to the phobogenic stimuli (Jones, 1924) and desensitize them (Wolpe, 1958); it was then associated with cognitive therapy to treat depression in the 1950s by identifying and modifying thought processes. The use of CBT in the treatment of psychosis was first studied in the mid-20th century.

Cognitive behavioral therapy (CBT) targets integrated disorders, i.e. reasoning biases and behavior disorders. By causing the development and retention of unfounded and delusional beliefs on reality, biases are the processes of jumping to conclusion, conferring more weight on uncontrollable and foreign causes for negative events and perceiving a threat in non-hostile environments (Freeman, 2007). Cognitive Behavioral Therapy (CBT) is composed of distinct treatment methods, sometimes sharing a few principles. In our experience, these basic principles can be applied to 22q11.2DS (see Table 2: CBT principles).

Psychotic symptoms development and retention are fostered by somehow basic alteration of information processing. The relationship between the cognitive phenotype and the development of psychotic symptoms in 22q11.2DS is well documented. The most basic alterations in 22q11.2DS, such as attentional and/or facial emotion deficits in themselves, are a risk factor for psychotic disorders (hallucinations and paranoid delusions) (Biswas and Furniss, 2016).

In 22q11.2DS, CBT-targeted behavior disorders may take the form of social avoidance and withdrawal or, in the contrary, a more unusual disinhibition and aggressiveness. In our experience, other negative symptoms observed in 22q11.2DS, such as motivation deficit or anhedonia, may also be reduced by CBT. Non-medicated treatments are particularly relevant in 22q11.2DS patients with psychotic symptoms, since antipsychotics may have serious adverse effects on them.

Depending on clinical needs, CBT is performed in individual or group sessions. In the context of psychotic disorders, as observed in 22q11.2DS, CBT may target relationship modalities, cognitive biases and/or hallucinations and associated beliefs, and delusional beliefs (Roberts and Penn, 2009). Individual CBT generally consists of 20–40 sessions spread over 4–8 months. Group CBT is most often performed in 10–15 weekly sessions. Group therapy is not as customized as individual sessions, but facilitates the exchange of adaptation strategies between participants and the reduction of psychotic symptoms (Wykes et al., 1999). Thus the patients feel they are not the only ones having these experiences; this point is very important for patients with 22q11.2DS and should be highlighted. Self-esteem defect remains a core symptom in 22q11.2DS (Tang et al., 2014) and, as such, an important CBT effect is self-esteem reinforcement, whether the therapy is individual or in group. Moreover relaxation is often used to reduce the impact of comorbid anxiety or, on a larger scale, to help patients control their emotions and prepare them to do behavior exercises or a cognitive effort. Anxiety disorders are more prevalent than mood disorders at every age, but especially in children and adolescents with 22q11.2DS. Daily living skills are predicted by the presence of anxiety disorders (Schneider et al., 2014).

CBT and other non-medicated treatment tools (such as cognitive remediation) for personal resources reinforcement are often used concomitantly. These therapeutic methods are called rehabilitation tools, i.e. non-medicated treatments used to restore the patient's skills and/or help them make a better use of their own skills on the way to recovery. The choice of cognitive remediation program to associate with CBT depends on which skills require reinforcement to increase autonomy (Demily and Franck, 2008).

However, use of psychoeducation (Xia et al., 2011) is mandatory. It provides basic essential information to help the patient recognizing and understanding the symptoms. The Stress-Vulnerability

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