

【総説】

A Literature Review on 22q11.2 Deletion Syndrome
The need for patient and family care management in Japan

22q11.2欠失症候群に関する文献レビュー
—日本における患者と家族へのケアマネジメントの必要性—

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Abstract

22q11.2 deletion syndrome (22q11.2DS) is a genetic disorder that can affect almost every organ and system in the body. The highly variable nature of expression and severity has contributed to both clinical and public under-recognition. A literature review was conducted to gain a current understanding of the main characteristics of 22q11.2DS and the implications for long-term management of this complex multi-system genetic disorder over the lifetime of the affected individual. From a search of Japan Medical Abstract Society, CINAHL, MEDLINE and Google Scholar databases 16 studies were identified as being relevant to the goals of the review. A content analysis of the studies focusing on the key areas of definition of 22q11.2DS, testing and diagnosis, clinical diagnosis, presentations and management was conducted. The results clarified the need for multi-disciplinary, coordinated management systems to support effective long-term care of 22q11.2DS affected individuals and their families. The findings lead to the conclusion that it is necessary to identify and develop suitable support systems for 22q11.2DS patients and their families in Japan.

Keywords: 22q11.2 deletion syndrome, Japan, support system, long-term management

キーワード: 22q11.2欠失症候群、日本、サポートシステム、長期的なマネジメント

I. Introduction

22q11.2 deletion syndrome (22q11.2DS) is a genetic disorder that can affect almost every organ and system in the body with the potential presence of both congenital and later onset manifestations in affected individuals. (Solot,

Gerdes, *et al.* 2001, Butcher, Chow, *et al.* 2012). The highly variable nature of expression has contributed to clinical under-recognition (Bassett, McDonald-McGinn, *et al.* 2011). Yet considering 22q11.2DS is the most common microdeletion syndrome in humans (Habel, Herriot, *et al.* 2014, Fung, Butcher, *et al.* 2015, Butcher, Chow, *et al.* 2012, Gothelf, Feinstein, *et al.* 2007) it is surprising that there is not greater awareness of this genetic disorder in clinical settings as well as within the wider community. Estimated prevalence is most

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often reported as 1 in 4000 live births (Bassett, McDonald-McGinn, *et al.* 2011, Baker and Skuse 2005, Bassett, Chow, *et al.* 2009, Yi, Tang, *et al.* 2013). Researchers (McDonald-McGinn, Emanuel and Zakai 2013, Solot, Gerdes, *et al.* 2001, Bassett, McDonald-McGinn, *et al.* 2011) have pointed out that as ascertainment rates improve the incidence may be higher. Perhaps reflecting an improved detection rate, Fung, Butcher, *et al.* (2015) report that the syndrome is estimated to affect up to 1 in 2000 live births. According to figures released by the Ministry of Health, Labour and Welfare, there were 1,037,231 live births in Japan in 2012. If the incidence rate is ranged between 1:4000 and 1:2000 births, then in that year alone there was a statistical likelihood that between 259 and 518 children were born with 22q11.2DS. With present-day treatment, survival past infancy to adulthood is now the norm, despite an elevated risk of premature death in adults with 22q11.2DS (Fung, Butcher, *et al.* 2015, Bassett, Chow, *et al.* 2009). This implies a growing population of affected individuals who progress through life in society.

This literature review was conducted to gain a current understanding of the main characteristics of 22q11.2DS and the implications for management of this complex multisystem genetic disorder over the lifetime of the affected individual. Within the 22q11.2DS-related literature, no studies emanating from Japan related to the goals of this review could be located, leaving this area wide open for future domestic research.

II. Method

A literature review was conducted to gain a current understanding of the main characteristics of 22q11.2DS and the implications for management of the disorder over the lifetime of the affected individual in Japan. Three databases (Japan Medical Abstract Society, CINAHL, and

MEDLINE) were searched for relevant literature between the years 1991 and 2015. The keywords used to search were: 22q11.2 deletion syndrome; congenital heart disease; schizophrenia; family; learning. The keyword search yielded 31 studies within the CINAHL and MEDLINE databases, of which 10 were relevant to the goals of the review. No relevant studies within the Japan Medical Abstract Society database were identified. A supplementary search was then carried out in order to elicit results that reflect the life-time development and management issues of the disorder. A further 6 studies relevant to the goals of the review were identified through this supplementary search using Google Scholar. Keywords were: 22q11.2 deletion syndrome; children; adolescents; adults; management; guidelines. The selected literature was then summarized with reference to the following categories: 1) Topic; 2) Authors, year of publication and title; 3) Location; 4) Aims, methods and findings; 5) Comments. A content analysis of the selected literature was conducted to gain an understanding of the general characteristics of 22q11.2DS including definitions, testing and diagnosis, clinical diagnosis, presentations as well as current recommended practices related to management.

III. Results

1. A summary of the selected literature for this review including 1) topic; 2) authors, year of publication and title; 3) location; 4) aims, methods and findings; 5) comments is presented in Table 1 below.

2. Content analysis

- 1) Definition of 22q11.2DS

22q11.2DS is a genetic syndrome associated with a microdeletion of DNA (ranging from 1.2 to 3 megabases) on the long arm of chromosome 22.

Table 1. A summary of the selected literature for this review

N	Topic	Authors (Year published) Title	Location	Aims, methods and findings	Comments
1	Overview of 22q11.2DS	McDonald-McGinn, Emanuel, Zackai (revised 2013) <i>22q11.2 deletion syndrome</i>	Philadelphia, USA	Descriptive overview of presentation and indicated management of 22q11.2DS. Updated in 2013 to reflect current research findings and recommendations. Details disease characteristics, its variable multi-system presentations, testing and diagnosis and management. Recommends multidisciplinary team approach including involvement of multiple departments, treatment of manifestations, surveillance and preventative care, educational and communication interventions and early diagnosis and intervention for psychiatric illnesses. Genetic counseling also stressed.	Details the varied phenotype and associated disorders patients present, along with management and surveillance practices. A good overview to grasp the multisystem nature of this disorder.
2	Psychiatric disorders in 22q11.2DS	Armando, Papaleo, Vircari (2012) <i>COMT implication in cognitive and psychiatric symptoms in chromosome 22q11 microdeletion syndrome: A Selective Review.</i>	Rome, Italy	Selective literature review of role of COMT in psychiatric symptoms of 22q11.2DS patients. This study investigates the gene catechol-O-methyl transferase (COMT) which is involved in the catabolic clearance of dopamine. COMT is affected by the 22q11.2 microdeletion. Finds no clear relationship between variation at COMT and schizophrenia in 22q11.2DS patients. However there may be a link between COMT and attention deficit hyperactivity disorder (ADHD) and Obsessive Compulsive Disorders (OCD). Recommends early interventions for high risk 22q11.2DS children.	Investigates the genetic mechanisms behind high prevalence of psychiatric disorders in 22q11.2DS patients. High morbidity rate for psychopathology in 22q11.2DS patients suggests genetic mechanisms are involved in development of psychiatric disorders. "Early intervention in the subgroup of children with sub-threshold signs of psychosis may reduce the risk of the development of psychotic disorders in adolescence." (p.279)
3	Psychiatric disorders in 22q11.2DS (various ages)	Tang, Yi, et al. (2013) <i>Psychiatric disorders in 22q11.2 deletion syndrome are prevalent but under-treated.</i>	Philadelphia, USA	Characterizes the prevalence and treatment of psychiatric illnesses in 22q11.2DS patients. 112 22q11.2DS patients of various age ranges recruited through 22q and you center were tested and interviewed (K-SADS & SIPS) + analysis of patient history to assess for major psychiatric disorder phenotypes. Results show 79% of individuals display psychopathology. 40% of patients receive on-going mental health care.	Psychopathology is common but not adequately treated. Recommends frequent assessment implying the need for patients to be followed by a mental health specialist.
4	Psychiatric disorders in 22q11.2DS (children)	Vorstman, Morcus, et al. (2006) <i>The 22q11.2 deletion in children: High rate of autistic disorders and early onset of psychotic symptoms.</i>	Utrecht, The Netherlands	60 individuals with 22q11.2DS (age 9-20) were studied to investigate 1) diagnose psychiatric disorders in 22q11.2DS children as potential markers of an increased vulnerability for schizophrenia in adulthood. 2) the extent to which psychiatric comorbidity is associated with IQ and cognitive functioning. Results: High rate of Autism Spectrum Disorders (50%) and psychosis (11.7%). 67% of participants had one or more psychiatric disorders with early age onset psychotic symptoms (often before 14 years of age). No clear correlation between incidence of psychotic disorder and cognitive function was established. 22q11.2DS children have an increased a priori risk of autism spectrum disorders, mild impairments in communication, socialization and repetitive behaviours necessitating careful monitoring.	The drive for social engagement is often present but the manner in which the social contacts are initiated or maintained is often problematic. "Our clinical experience with this population suggests that specifically the social abilities of these children tend to be overestimated. This leads to chronic exposure to a too-demanding environment, which in turn may be associated with secondary psychopathology." (p.1111) Recommends systematic psychiatric examination for all 22q11.2DS children preferably before age 10.
5	Psychiatric disorders in 22q11.2DS (children)	Aneja, Fremont, et al. (2007) <i>Manic symptoms and behavioral dysregulation in youth with velocardiofacial syndrome (22q11.2 deletion syndrome).</i>	New York, USA	This study investigates the extent to which 22q children exhibit manic symptoms and how those symptoms manifest in behavioral dysregulation. 86 children with 22q11.2DS and 36 community controls. Assessed manic symptoms using instruments that distinguish manic behaviors from ADHD and depression. Results showed groups did not significantly vary in manic symptoms shown, but 22q11.2DS children varied from control group in some subscales of the Child Behavior Checklist (CBCL), including somatic complaints, social problems and thought problems.	It was found that 22q11.2DS children with manic symptoms are at greater risk of continued psychiatric problems than children from the general population who exhibit manic symptoms. Recommends early assessment, diagnosis and treatment of manic symptoms in 22q11.2DS patients to mitigate possible further psychiatric deterioration.
6	Psychiatric disorders in 22q11.2DS (children)	Yi, Tang, et al. (2013) <i>Contribution of congenital heart disease to neuropsychiatric outcome in school-age children with 22q11.2 deletion syndrome.</i>	Philadelphia, USA	Investigates the extent of CHD contribution to the high prevalence of psychiatric disorders and neurocognitive deficits. 54 children with 22q11.2DS and a control group of 16 aged matched non-deleted children were assessed through interviews and tests. Results show no significant causal relationship between CHD and psychiatric disorders, leading to the conclusion that 22q11.2DS itself may confer higher risk of neuropsychiatric disorders.	Investigates the CHD mechanisms behind high prevalence of psychiatric disorders in 22q11.2DS patients. Notes that CHD raises the rate of anxiety disorders in both 22q11.2DS and non-22q11.2DS populations alike. No significant difference was observed between control group and 22q11.2DS group in terms of CHD contribution to neuropsychiatric disorders.

N	Topic	Authors (Year published) Title	Location	Aims, methods and findings	Comments
7	Psychiatric disorders in 22q11.2DS (adolescents)	Baker and Skuse (2005) <i>Adolescents and young adults with 22q11 deletion syndrome: psychopathology in an at-risk group.</i>	London, UK	Adolescent case-control study aiming to characterise 22q11.2DS comorbid psychopathology and compare with idiopathic schizophrenia development trajectories to predict premorbid features. 25 individuals with 22q11.2DS and a gender, age and estimated IQ matched comparison group of 25 individuals with low average general ability or mild/moderate learning disability were investigated. Semi structured interviews using CAPA (Angold, <i>et al.</i> 1995) were analysed to diagnose symptoms and symptom counts. Results show individuals with 22q11.2DS display diverse psychiatric symptoms, especially mood disruptions, attention deficits and psychotic phenomena. Premorbid social and occupational functioning was significantly impaired in comparison with the control group. There was no relationship between IQ and psychopathology.	Previous studies of psychiatric disorder in individuals with 22q11.2DS focused on younger children. No significant differences between case-control groups were found. This might be explained by the age. Children may not be able to self-report psychotic disturbances at a young age, and parents/caregivers would be unaware of such disturbances. Another reason might be that developmental processes relevant to the emergence of later psychotic disturbances have their onset in adolescence. Clinical implications: Adolescents and young adults with 22q11.2DS experience diverse psychiatric symptoms discoverable only by personal interview. Predictive power of schizotypal phenomena not highly accurate in determining future adult-onset illness. Schizotypal phenomena affect up to half of adolescents with 22q11.2DS.
8	Psychiatric disorders in 22q11.2DS (adolescents)	Gothelf, Feinstein, <i>et al.</i> (2007) <i>Risk factors for the emergence of psychotic disorders in adolescents with 22q11.2 deletion syndrome.</i>	Petah Tiqwa, Israel	This longitudinal study of 60 adolescents (31 with 22q11.2DS and 29 with idiopathic developmental disability control group) aims 1) to investigate psychiatric, behavioral and adaptive developmental trajectories of 22q11.2DS group in comparison to control group and 2) to identify early risk factors for psychotic disorders in 22q11.2DS. Results show that 22q11.2DS children exhibit more severe psychiatric symptoms than control group as they pass through adolescence. Findings indicate that for individuals with 22q11.2DS there is a continuity and gradual exacerbation of psychotic symptoms from childhood to young adulthood.	"22q11.2DS is the most common known genetic risk factor for the development of schizophrenia." (p.663). Clinical implications: children with 22q11.2DS should be carefully and routinely screened for early signs of mild psychotic manifestations. Because high risk symptoms such as OCD are not as socially disruptive as some other symptoms such as ADHD, they tend to be overlooked, but these internalized symptoms are a better indicator of later development of psychotic disorders. (p.668). Anxiety disorders and OCD in particular are robust early childhood indicators for the later development of psychosis in individuals with 22q11.2DS.(p.668).
9	Psychiatric disorders in 22q11.2DS (adults)	Bassett, Hodgkinson, <i>et al.</i> (1998) <i>22q11.2 deletion syndrome in adults with schizophrenia.</i>	Toronto, Canada	This paper aims to clarify the association between psychotic disorders and 22q11.2DS. Delineation of an adult phenotype would help to increase the probability of identifying 22q11.2 deletion related syndromes in adults. 10 adults diagnosed with schizophrenia and presenting with 2 or more characteristic features of 22q11.2DS were clinically investigated "The findings suggest that investigating patients with schizophrenia, if they have other syndromic features, may identify adults with a 22q11 deletion." (p.6) Patients thus identified did not present with high rates of cardiac or palatal malformations seen in 22q11.2DS patients ascertained through pediatric clinics. In other words undiagnosed 22q11.2DS patients probably exist in adult psychiatric populations due to presenting with mild clinical physical phenotypes.	The main implication of this study is that undiagnosed 22q11.2DS patients probably exist in adult psychiatric populations due to presenting with mild clinical physical phenotypes. Adults identified with 22q11.2DS in psychiatric populations require follow-up for associated physical conditions and genetic counselling should be offered. Conversely children with 22q11.2DS should be monitored for early signs of psychotic illness, since early intervention has been shown to lead to improved functioning.
10	Endocrinology and intellectual disability in 22q11.2DS (neonatal)	Cheung, George, <i>et al.</i> (2013) <i>Neonatal hypocalcemia, neonatal seizures, and intellectual disability in 22q11.2 deletion syndrome.</i>	Toronto, Canada	In recognition of the high prevalence of hypocalcemia in 22q11.2DS patients, this study investigates, using a logistic regression model, the extent of the relationship between neonatal hypocalcemia and long term intellect in 149 22q11.2DS adult patients. Findings show that neonatal hypocalcemia and neonatal seizures are strong predictors of intellectual level.	Results suggest neonatal hypocalcemia and neonatal seizures in 22q11.2DS patients are associated with moderate to severe intellectual disability. Neonatal hypocalcemia is not often recognised in infants until after seizures, when the damage is already potentially done. Recommends screening for 22q11.2DS after 5-7 days of life. Or if neonatal hypocalcemia or neonatal seizures are observed, infants should be screened for 22q11.2DS. Such measures could prompt meaningful anticipatory care.

N	Topic	Authors (Year published) Title	Location	Aims, methods and findings	Comments
11	Communication and 22q11.2DS (children)	Solot, Gerdes, <i>et al.</i> (2001) <i>Communication issues in 22q11.2 deletion syndrome: Children at risk.</i>	Philadelphia, USA	Investigates correlation between 22q11.2DS children and speech and communication deficiencies. A large population of pre-school and school age children with 22q11.2DS was evaluated by a team of medical and developmental specialists. Results reveal a wide range of communication deficiencies in children with 22q11.2DS, including delayed language emergence and prolonged periods between milestones; speech and language disorders that continue into school age; hypernasality related to palate anomaly even after medical fixation.	Recommends “every child with 22q11.2DS should be considered at risk and should therefore be enrolled in early intervention settings as soon as a diagnosis is made. A proactive stance is recommended in the management of these patients” (p.70).
12	Social functioning in 22q11.2DS (adults)	Butcher, Chow, <i>et al.</i> (2012) <i>Functional outcomes of adults with 22q11.2 deletion syndrome.</i>	Toronto, Canada	Investigates impact of 22q11.2DS on functional outcomes of adult patients in society. 100 adults with 22q11.2DS were investigated using Vineland Adaptive Behavior Scales to assess social functioning. Findings confirm widespread functional deficits that have an impact on most major aspects of social life. Few 22q11.2DS patients were self-supporting financially. Relative strengths were found in activities of daily living and in performance of suitable employment.	Recommendations include patients, families and health-care providers using these findings to develop reasonable expectations and long-term goals, and to inform interventions that improve functioning and increase independence. Highlights the need for increased vocational and social support services for 22q11.2DS adults.
13	Adult mortality and 22q11.2DS	Bassett, Chow, <i>et al.</i> (2009) <i>Premature death in adults with 22q11.2 deletion syndrome.</i>	Toronto, Canada	Investigates hypothesized elevated mortality rate. 102 22q11.2DS adults (>17years old) were followed. 12 deaths were observed (11.8%). Average age of patients at death was 41.5 years. (range 18.1-68.6) The most common cause of death observed was unexplained sudden death (6%).	Data supports elevated risk of premature death in adult 22q11.2DS patients irrespective of presence of CHD. Causes unspecified but likely multifactorial.
14	22q11.2DS management guidelines	Bassett, McDonald-McGinn, <i>et al.</i> (2011) <i>Practical guidelines for managing patients with 22q11.2 deletion syndrome.</i>	Toronto, Canada	This paper proposes a set of guidelines designed to assist primary care physicians and includes recommendations for anticipatory care management of 22q11.2DS. Guidelines were developed from the findings of 2 international consensus meetings and an extensive literature review. Guidelines are presented in 3 tables in addendum: Table 1 multi-system features presented, along with management recommendations. Table 2: at diagnosis list of recommended assessments as well as timetable of lifespan development related assessments. Table 3: List of cautions and considerations for treatment of those diagnosed with 22q.	The paper begins with a very good case presentation of the complicated course of presentations showed by a 12 year old 22q11.2DS patient since birth. Explains variable spectrum and expressivity, and multi-system nature of syndrome. The paper presents a rationale for clinical centres of excellence. The proposed guidelines do not take into account practical costs of an anticipatory multi-system care, so they may be considered as an idealistic list of recommendations.
15	22q11.2DS management guidelines	Habel, Herriot, <i>et al.</i> (2014) <i>Towards a safety net for management of 22q11.2 deletion syndrome: guidelines for our times.</i>	London, UK	Describes presentations and management practices of 22q11.2DS Gives clear clinical definition of the size and location of 22q11.2 deletion.(p.758) The disorder occurs spontaneously in 85-90% of patients or is inherited from either parent in an autosomal dominant fashion. Presents guidelines for a holistic, multidisciplinary anticipatory approach to management. Guidelines were drawn up from a consensus document with participatory input from parents, clinicians and therapists with experience in managing the condition. Recommendations presented in tables. Table 1 Recommendations for investigation, management and referral. Table 2: Therapeutic, psychological, behavioural and educational assessments for early intervention. Table 3: Regular assessments for all individuals. Table 4: Advocacy.	Minimum rather than optimal recommendations reflect recognition of limited resources in health care systems. The paper comments on diagnostic complexity due to wide variability in this multi-system disorder. Detection rates improve when specialists are familiar with the disorder. Fetal anomaly screening may result in identifying 22q11.2DS at the fetal stage. The most common diagnostic tool is FISH which is 95% effective in detecting deletions, but is not always able to detect atypical deletions. Now becoming superseded by other tests such as “array comparative genome hybridisation (aCGH), genome-wide microarrays and multiplex ligation-dependent probe amplification (MLPA).
16	22q11.2DS management guidelines (adults)	Fung, Butcher, <i>et al.</i> (2015) <i>Practical guidelines for managing adults with 22q11.2 deletion syndrome.</i>	Toronto, Canada	Describes developments, issues and concerns pertaining to adults with 22q11.2DS especially neuropsychiatric, endocrine, cardiovascular, reproductive and psychosocial issues. Guidelines were developed from the findings of an extensive literature review and the recommendations from an international panel of experts based upon a draft consensus document. Table 1: recommendations for periodic assessment and health monitoring for adults with 22q11.2DS. Table 2: signs and symptoms representing a change from baseline that might suggest a treatable psychiatric illness. Table 3: general recommendations for prenatal and perinatal care of adults with 22q11.2DS. Table 4: genetic counselling strategies.	Outlines at risk areas and issues surrounding adults with 22q11.2DS functioning within society (e.g. communication and socializing, financial and other competency-related decision making, vocational opportunities, sexual health and reproduction, etc.) Many adults who have milder presentations of 22q11.2DS are only diagnosed after the birth of an affected child or through genetic screening of at risk populations.

(McDonald-McGinn, Emanuel and Zackai 2013, Vorstman, Morcus, *et al.* 2006, Aneja, Fremont, *et al.* 2007). In most cases the deletion is heterozygous (Armando, Papaleo and Vicari 2012). The deletion occurs spontaneously in 85-90% of affected individuals, or is inherited from either parent in an autosomal dominant fashion (Habel, Herriot, *et al.* 2014, Bassett, McDonald-McGinn, *et al.* 2011). To date, no correlation between the size or site of the deletion and phenotype has been established (Habel, Herriot, *et al.* 2014).

2) Testing and diagnosis

Since 1992, 95% of microdeletions have been detected using fluorescent in situ hybridization (FISH) (Habel, Herriot, *et al.* 2014). In fact, it was the advent of FISH that allowed clinicians to recognize other apparently different syndromes (DiGeorge syndrome, Velocardiofacial syndrome, conotruncal anomaly face syndrome, Cayler cardiofacial syndrome) are often tied to a 22q11.2 deletion (Bassett, McDonald-McGinn, *et al.* 2011). FISH is less likely to detect very small or atypical nested microdeletions, and is being superseded by more sophisticated techniques such as multiplex ligation-dependent probe amplification (MLPA) or array comparative genomic hybridisation (aCGH) that reveal atypical deletions and can detect 22q11.2 deletions of any size (Bassett, McDonald-McGinn, *et al.* 2011, Habel, Herriot, *et al.* 2014).

3) Clinical diagnosis

Bassett, McDonald-McGinn, *et al.* (2011) state "Identification of 22q11.2DS, especially in adolescents and adults, often requires an enhanced index of suspicion." (p.3) The tell-tale clinical features that most often prompt a clinical investigation for 22q11.2 deletion vary, but usually include two or more of the following so called 'classic findings': developmental disabilities, learning disabilities, conotruncal cardiac

anomalies, palatal defects, nasal regurgitation and or hypernasal speech, behavioural problems, psychiatric illness, immunodeficiency, hypocalcemia and characteristic facial features. (Bassett, McDonald-McGinn, *et al.* 2011) The multisystem nature of the disorder combined with variable expression and severity and the multitude of possible combinations can obscure a clear clinical diagnosis.

4) Presentations

A fuller description of the presentations and their percentage occurrence rate is available elsewhere (McDonald-McGinn, Emanuel and Zackai 2013). In describing such a variable phenotype, most researchers refer to broad headings to categorize the many possible presentations of 22q11.2DS.

Habel, Herriot, *et al.* (2014) offer a short summary of presentations that typifies descriptions given by many researchers:

The major conditions occurring in approximately 70% or more are congenital heart disease, immune deficiency, palate defects affecting feeding and speech and learning difficulties. Those found in 25%-50% include feeding disorders, early growth faltering, gut dysmotility, psychiatric, behavioural and neurological conditions, structural (renal, skeletal, brain, gastrointestinal, eye and dental) abnormalities, hearing impairment, hypocalcemia, haematological and autoimmune disorder.

The individual with 22q11.2DS is likely to present changing clinical and psychosocial priorities from birth to maturity. Early care is dominated by organ malformations requiring surgery, feeding support, and treating

infections, as childhood progresses, neurodevelopment, behavioural and educational priorities require attention, in adolescence, scoliosis monitoring with possible surgical intervention, and psychosocial support; in adults socioeconomic, general medical and psychiatric support. (pp.758-759)

Habel, Herriot, *et al.* (2014) go on to comment that facial dysmorphism (long narrow face, almond shaped eyes, bulbous nose with a flat tip, small mouth, overfolded ear helix, asymmetry of facial movement) becomes more pronounced in adolescence but is often subtle in both infants and adults.

The high morbidity in individuals with 22q11.2DS of psychiatric symptoms and disorders such as attention deficit hyperactivity disorder and obsessive compulsive disorders and schizophrenia has led to a number of recent studies focusing on neuropsychiatric diseases that comprise the most common group of later-onset conditions in 22q11.2DS (e.g. Tang, Calkins, *et al.* 2013, Yi, Tang, *et al.* 2013, Baker and Skuse 2005, Gothelf, Feinstein, *et al.* 2007, Bassett, Hodgkinson, *et al.* 1998). These conditions are often of great concern to affected individuals and their families because of their effect on social functioning and the associated stigma (Fung, Butcher, *et al.* 2015). Children may not be able to self-report psychotic disturbances when young, and from their external point of view parents would most likely remain unaware of such disturbances (Baker and Skuse 2005), but children with 22q11.2DS should be carefully monitored for early signs of psychotic illness as early intervention is known to lead to improved functioning (Bassett, Hodgkinson, *et al.* 1998).

Ongoing communication issues have been documented that stem from both physical and

psychological causes. Palate and facial anomalies often cause hyper-nasality even after corrective surgery, and delayed emergence of language and prolonged periods between language development milestones are common (Solot, Gerdes, *et al.* 2001). Researchers have noted that 22q11.2DS affected individuals have often exhibited learning disabilities characterised by a weakness in mathematical skills and where performance IQ is lower than verbal IQ (McDonald-McGinn, Emanuel and Zackai 2013, Solot, Gerdes, *et al.* 2001). Communication disorders are widely reported, and are often evident from an early stage and persist through the life-time of the affected individual, prompting Solot, Gerdes, *et al.* (2001) to comment that such communication disorders this “may constitute one of the most psychosocially difficult aspects of the deletion for patients and their families” p.67)

Adults present with widespread functional deficits that have an impact on most major aspects of social life. Relative strengths were observed in performance of activities of daily living and in employment situations suited to the individual (Butcher, Chow, *et al.* 2012).

5) Management

As 22q11.2DS is a genetic disorder, genetic counseling is indicated upon diagnosis. Such counselling would involve discussions on prevalence, etiology, detection, variability, interventions, transition issues and reproductive decision making. (Fung, Butcher, *et al.* 2015, Habel, Herriott, *et al.* 2014, McDonald-McGinn, Emanuel and Zackai 2013) Long-term management requires careful monitoring, and a holistic anticipatory approach. Guidelines describing management practices have been published (Fung, Butcher, *et al.* 2015, Habel, Herriott, *et al.* 2014, Bassett, McDonald-McGinn, *et al.* 2011). By and large, indicated treatments of 22q11.2DS

associated manifestations do not differ from treatment of similar idiopathic phenotypes. However, with a high burden of comorbidity of medical and neuropsychiatric conditions affecting multiple systems, clinicians should pursue management strategies in a way that coordinates with other types of care an individual with 22q11.2DS might be receiving (Habel, Herriott, *et al.* 2014, Bassett, McDonald-McGinn, *et al.* 2011).

IV. Discussion

22q11.2DS is common and the number of affected individuals is likely to increase as medical advances extend survival through to adulthood. The multisystem nature and associated array of comorbid presentations means that an individual with 22q11.2DS may be seen by a multitude of clinicians over a lifetime to deal with seemingly separate conditions, but which are causally linked to 22q11.2DS. Early diagnosis provides the best chance to positively affect the course of the illness. Experts recommend anticipatory care, including screening for and coordinated management of associated conditions. Specialized 22q11.2DS clinical centers have been established in a number of locations to provide multidisciplinary, personalized, and ongoing support for affected individuals and their families (for example, 22q and You Center, The Children's Hospital of Philadelphia, Philadelphia, USA, 22q Center at Nationwide Children's Hospital, Ohio, USA, The Dalglish Family Hearts and Minds Clinic For Adults with 22q11.2 Deletion Syndrome, Toronto, Canada). Such centers can facilitate a coordinated management approach as well as providing information and access to professional and peer support networks and support organizations and foundations for patients and families. As yet, few such centers exist in the world, and there are no such centers in Japan where the burden of responsibility for coordinating management rests

mostly on the shoulders of the family of the individual with 22q11.2DS or the individual him or herself later on in life. A peer support group of 22q11.2DS affected families is active in Japan, even recently releasing their own guidebook for families dealing with the syndrome (22 Heart Club 2014), but there is as yet little in the way of systematically coordinated medical professional help or public recognition of the syndrome. The significant social stigma attached to genetic conditions, intellectual disability and psychiatric disorders in Japan is a barrier to progress in this respect. While the issues of lack of public awareness and social stigma are often tackled head on in the form of public education campaigns, press releases and open public forums in many countries, in Japan there is a palpable reticence, even on the part of affected families, even within support groups such as 22 Heart Club, to disclose information about 22q11.2DS publicly. The situation regarding patient and family support in Japan clearly needs to be investigated with a view to developing appropriate long term support systems for individuals affected by 22q11.2DS and their families.

V. Conclusion

In Japan there is very limited public and medical professional recognition of the 22q11.2DS, yet statistically there is likely a significant population of both diagnosed and non-diagnosed individuals who are affected by the syndrome. In order to gain a current understanding of the main characteristics of 22q11.2DS and the implications for management of this complex multisystem genetic disorder over the lifetime of the affected individual, a literature review of 16 studies from various countries outside of Japan was conducted. The studies were summarized and presented in the attached table. A content analysis of the studies was conducted and the results pointed to the need for the development

of systems of 22q11.2DS patient and family long-term support suitable to the situation in Japan. Further investigations will be required to identify the specific support needs of individual patients and their families within the Japanese context and systems that can be put in place to answer those needs.

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22q11.2欠失症候群に関する文献レビュー —日本における患者と家族へのケアマネジメントの必要性—

抄録

22q11.2欠失症候群は、22番染色体の微細欠失により広範囲にわたる症状が出現する遺伝性の疾患である。また、遺伝子欠損の発現型と重症度にかなりばらつきがあるため、臨床現場でも一般社会でも未だ認識されないままとなっている。この文献レビューは22q11.2欠失症候群の主たる特徴について最新の理解と、この複雑な遺伝性疾患患者に対しての長期的なマネジメントのための示唆を得ることを目的とした。医学中央雑誌、CINAHL、MEDLINE、そしてGoogle Scholarから、今回のレビューの目的に沿うものが16件見つかった。22q11.2欠失症候群の定義、検査と診断、臨床診断、症状、マネジメントに注目してそれらの文献の内容分析を行った。結果、22q11.2欠失症候群をもつ人々と家族に対する効果的な長期的ケアをサポートするために、多くの専門分野にわたる協調的なマネジメントシステムの必要性が明らかとなった。これらの知見から、22q11.2欠失症候群をもつ人々とその家族のための、日本の状況に適した支援システムの特定・開発の必要性が強く示唆された。