

Clinical Psychopharmacology and Neuroscience - Manuscript

Submission

- **Manuscript ID:** CPN-21-877
- **Title:** Psychiatric comorbidities in adults with DiGeorge Syndrome
- **Running Title:** DiGeorge Syndrome and psychiatric comorbidities
- **Article Type:** Original Article
- **KeyWords:** CATCH-22, Psychiatric comorbidities, DiGeorge

Psychiatric comorbidities in adults with DiGeorge Syndrome

ABSTRACT

Introduction:

DiGeorge Syndrome (DGS) is a common multisystem disorder associated with deletions on chromosome 22q11.2. Our objective is to evaluate the psychiatric comorbidities and demographics of patients suffering from DGS in a nationally representative dataset on inpatient hospitalizations.

Methods:

The Nationwide Inpatient Sample (NIS) for the year 2005-2017 was used for this study. Data on patients with DiGeorge syndrome were collected by using the ICD code. Univariate and multivariate logistic regression analysis was performed.

Results:

In our study, the average age was 30.4 years (n=6563), with 59.9% male, and 61.8% of patients were white. There was a high prevalence of mood disorders (24.7%) and anxiety disorders (16.4%), followed by schizophrenia and other psychotic condition (14.0%). In patients with mood disorders, 8% had Major Depressive Disorder, and 7% had bipolar depression. Overall composite of psychiatric comorbidities was present in 2959 (45.1%) of patients. The mean length of stay was 6.58 days, and 77% of patients had routine discharge to home. In the adjusted analysis, the average length of stay was 8.6 days vs. 6.7 days (p <0.001) in patients with and without psychiatry comorbidities. In comparison to routine discharge, patients with psychiatry comorbidities were more likely to be discharged to other healthcare facilities (OR: 1.28, p <0.001) and discharged against medical advice (OR: 3.45, p<0.001).

Conclusion:

Patients with DGS have worse outcomes with a higher rate of discharge to other healthcare facilities and a higher rate of being discharged against medical advice. Further large scale randomize studies are indicated.

Introduction

DiGeorge Syndrome (DGS) is a multisystem disorder due to deletions on chromosome 22q11.2 (1). It is one of the more common disorders of recurring copy number variants (CNV) has an estimated prevalence of 1 in 4000 live births (2). 90% of these deletions are the result of spontaneous events while the remaining 10% have an affected parent with no gender differences (3, 4, 5). Typical features include developmental disabilities, learning disabilities, cardiac malformations, oronasal abnormalities, endocrine and metabolic disturbances, typical facial features and behaviors and psychiatric comorbidities (6, 7). Psychiatric phenotype has been a focus of study due to their frequent and often pronounced presence in DGS (8). Common psychiatric comorbidities seen in DGS are anxiety disorder such as specific and social phobias, generalized anxiety disorder (GAD), attention-deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), schizophrenia, major depressive disorder, persistent depressive disorder (dysthymic disorder) and autistic disorders (ASD) (8,9). Psychiatric disorders are rare in children but relatively common during adulthood with a 40.7% prevalence of depressive disorders in young adults [18-24-year-old], 32.1% prevalence of psychotic disorders in adults 24 years or older (8). Fung et al. studied the prevalence of major psychiatric disorders in 40 individuals with DGS between ages 20 to 57 years and found 22.5% of the subjects had schizophrenia or schizoaffective disorder with a mean age of onset of 22 years. This is significantly higher than the general population with a prevalence of 1.2 % ($p < 0.0001$) (10). In a large on-going study that recruited 20 individuals (12 females and 8 males) between 5-33 years of age and with a confirmed diagnosis of DGS, 13 individuals had a diagnosis of ADHD and or ASD (11). In a serial study of 43 participants with DGS, Gothelf et al. identified 32.6% of the participants met full DSV-IV criteria for OCD (12). Using an inpatient hospital admission dataset, we studied the psychiatric comorbidities and demographics of patients with DGS. The

objective of this study is to evaluate the prevalence of psychiatric comorbidities in adults with DiGeorge Syndrome. We also looked at the factors associated with these comorbidities.

METHODS:

Data Source

For the purposes of this study we used the Nationwide/National Inpatient Sample (NIS) from the year 2005-2017. The NIS is part of the databases and software tools developed for the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality. The NIS dataset has 20% stratified random sample of all hospital discharges in the United States and it includes all patients irrespective of the insurance status (13). It has data on more than 7 million hospital stays. Each record contains information on primary (reason for hospitalization) and secondary diagnoses and procedures, patient demographic characteristics, hospital characteristics, expected payer, discharge status, length of stay, severity and comorbidity measures. Also, for each record discharge level weights are provided to obtain national estimates. The Institutional review board (IRB) approval was not required, as it does not contain protected health information (PHI).

Data collection

Data on patients with DiGeorge syndrome were collected from January 2005 to December 2017 by using diagnosis codes according to International Classification of Diseases, Ninth Revision, Clinical Modification/Procedure Coding System (ICD-9-CM) and International Classification of Diseases, Clinical Modification, Procedure Coding System (ICD-10-CM/PCS). Our targeted population was obtained by using ICD code 27911 and D821 in the primary (DX1) and

secondary diagnosis variables. Among this patient population, we used ICD code based on Clinical Classifications software of the NIS dataset (13) for mood disorder, anxiety disorder, schizophrenia and other psychotic disorder, adjustment disorder, personality disorder, ADHD and other conduct disorder, substance related disorder, alcohol related disorder, miscellaneous mental health disorders, and impulse control disorders.

Data were collected on age, gender, race, discharge disposition, comorbidities, hospital geographical region, and length of stay. In addition, we collected a data on severity of illness category from APRDRG_severity (All Patients Refined Diagnosis Related Groups Severity of illness subclass) variable. All Patient Refined DRGs (APR-DRGs) are assigned using software developed by 3M Health Information Systems. Severity of Illness defined as the extent of physiologic decompensation or organ system loss of function.

Statistical Analysis

Continuous data are presented as mean (standard error) and as counts and percent if categorical. Descriptive analysis was performed for patients aged ≥ 18 years and presented in a table format. Univariate and multivariate logistic regression analysis was performed to evaluate the variables associated with psychiatric comorbidities. In the multivariate analysis, age, sex, race and illness severity were included. For the length of stay analysis, adjustment was also performed for hospital characteristics (bed size, location and unique hospital identifier). Odds Ratio (OR) and 95 % confidence interval (CI) was generated for age, sex, race, severity of illness, discharge disposition and length of stay. Collinearity was assessed using variance inflation factors (VIFs). For variables with <5% missing data, the missing values were replaced with the dominant category (14). Missing value was considered as a separate category for race because of more than 5% of the data was missing. All tests were 2-sided, and a p-value <0.05 was considered

statistically significant. The statistical analysis was performed using the SPSS version 26.0 for Windows (IBM Software, Inc., Armonk, NY, USA).

Results

Average age was 30.4 years (n=6563) with 59.9% male and 61.8% patients were white. Baseline characteristics of the study population is shown in Table 1 and psychiatric comorbidities are shown in Figure 1. There was high prevalence of mood disorders (24.7%) and anxiety disorders (16.4%), followed schizophrenia and other psychotic condition (14.0%). In the patients with mood disorders, 8% had Major Depressive Disorder and 7% had bipolar depression. Suicidal ideation was present in 4.9% and suicidal attempt in 0.40% of patients. Majority of the patients (70%) had major to extreme loss of function based on illness severity categories. Substance related disorders were prevalent in 5.0% and alcohol related disorder were prevalent in 1.9% of patients. In total psychiatric comorbidities were present in 2959 (45.1%) patients. Despite high prevalence of psychiatric comorbidities, inpatient psychiatric admissions accounted for 13.3% (n=870) of the patients. Mean length of hospital stay was 6.58 days. The vast majority of patients (77%) had routine discharges to home. Death occurred in 1.9% (126) of patients.

Geographically, southern United States had the highest number of patients. Intellectual disability was prevalent in 16.5% (n=1084) of patients. There was a high prevalence of hypertension, hypothyroidism, chronic pulmonary disease, coagulopathy and valvular heart diseases in the study sample.

Factors associated with psychiatric comorbidities

To assess the variables associated with psychiatric comorbidities age, sex, race and illness severity were included in all the multivariate analyses (Table 2). Increase in age was associated

with psychiatric comorbidities (OR: 1.011, $p < 0.001$). Odds of having psychiatric comorbidities was greater for female compared to male (OR: 1.17, $p = 0.002$). In comparison to white, non-white race was associated with less psychiatric comorbidities (OR: 0.66, $p = 0.002$). There was no association between severity of illness and psychiatric comorbidities. In comparison to routine discharge, patients with psychiatric comorbidities were more likely to be discharged to other healthcare facility (OR: 1.28, $p < 0.001$) and discharged against medical advice (OR: 3.45, $p < 0.001$). There was an association between length of stay and psychiatric comorbidities ($p < 0.001$). In the adjusted analysis, average length of stay was 8.6 days vs. 6.7 ($p < 0.001$) in patients with and without psychiatric comorbidities. In addition, length of stay was longer for patients with psychiatric comorbidity as the primary diagnosis (11.4 days, vs 7.04 days, $p < 0.001$).

Discussion:

The present study discusses the prevalence of psychiatric comorbidities in adults with 22q11.2 deletion syndrome using Nationwide/National Inpatient Sample (NIS) for the years 2005-2017 with a sample size greater than six thousand ($N=6563$). To the best of our knowledge this is the largest study on the prevalence of psychiatric comorbidities in adults with DGS. The sample had an average age of 30.4 years (59.9% female and 61.8% of them Caucasian). Overall composite of psychiatric comorbidities was present in 2959 (45.1%) individuals.

Mood Disorders were more prevalent than anxiety disorders which is consistent with findings in previous studies. (8, 10). Of the subjects with Mood Disorders, 8 % had Major Depressive disorder. There was 7% prevalence of Bipolar Disorder which is different than prior studies which report prevalence at around 1.3%, similar to that of the general population. (17, 18).

According to previous studies, anxiety disorders (24%) are the most prevalent psychiatric comorbidity. (18) However, in this analysis, mood disorders were the most prevalent at 24.7% followed by anxiety disorders at 16.4%.

Our analysis shows a 14% prevalence of psychotic disorders, much lower than prior reports such as Schneider et al., who reported prevalence in emerging adults (18-25) at 23.53%, young adults (26-35) at 41.33%, and mature adults (age > 36 years) at 41.33%. (15) For suicidal behaviors we looked at suicidal ideations and attempts which were at 4.9% and 0.40% respectively. 3.4 % had ADHD which is similar to the general population prevalence of 4.4% (19) Data on prevalence of Intellectual Disability (ID) in individuals with DiGeorge syndrome is limited. In our study ID was present in 16.5 % subjects whereas data from the 2016 meta-analysis of international studies found the ID prevalence of adults in general population to range from 0.05 to 0.08% (20).

To the best of our knowledge, this is the first to provide information about the length of stay, loss of function and discharge disposition in patients with DiGeorge syndrome. Exploring the length of hospital stay is important for health care policymakers because the number of hospital days attributed to psychiatric conditions is greater than attributed to any other medical disorder (16). The average length of stay in this patient population was 6.58 days. In the adjusted analysis, the average length of stay was 8.6 days' vs 6.7 days ($p < 0.001$) in patients with and without psychiatry comorbidities. Moreover, the length of stay was longer for patients with psychiatric comorbidity as the primary diagnosis (11.4 days' vs 7.04 days, $p < 0.001$). We collected data on severity of illness category from APRDRG_severity (All Patients Refined Diagnosis Related Groups Severity of illness subclass) variable and compelling finding from our study is that 70.6% of patients with 22q11.2 syndrome had major to extreme loss of function based on severity of illness.

We looked into the discharge disposition and found the majority (70%) of individuals had a routine discharge while 20% were discharged to other health care facilities. In the multivariate analysis, we compared the discharge disposition of patients with psychiatry comorbidities versus without psychiatry comorbidities. In comparison to routine discharge, Patients with psychiatry comorbidities were more likely to be discharged to other healthcare facilities (OR: 1.28, $p < 0.001$) and discharged against medical advice (OR: 3.45, $p < 0.001$). To compare

Geographical distribution, we divided the United States into 4 geographical regions: The Northeast, Midwest, South, and West. The South had the highest reported cases at 34.10% while the northeast had the lowest reported cases at 18.20%.

We used the NIS as a nationally representative sample of patients diagnosed with DiGeorge syndrome. We applied sampling weights to generalize estimates for comorbidity prevalence. The inpatient outcomes are generalizable to a bigger population than the sample studied. The NIS data set was a large sample size because we included 6563 individuals with 22q11.2 syndrome. This dataset is subject to minimal reporting bias, and all information is coded independently of the individual practitioner, making it a potentially more reliable source. To our knowledge, this is the first study that reports information about the length of stay, geographical distribution and discharge disposition of patients with DGS.

The limitation for using hospitalization (and not patient) as the unit of analysis is that it is not generalizable to all patients with DiGeorge syndrome. There may have been under reporting of chronic comorbidities in the NIS data because the administrative database was used. Hence, clinical data were not incorporated into the data source. We recommend that future research examine the influence of psychiatric comorbidities with clinical data.

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Table 1. Baseline characteristic in adults

	Age \geq 18 years	
	N=6563	
	Number or Mean	Percentage (%) or
Age, mean, standard error	30.40	0.14
Female	3929	59.9
Race		
White	4055	61.80%
Black	720	11.00%
Hispanic	792	12.10%
Asian or Pacific Islander	123	1.90%
Native American	35	0.50%
Other/unknown	133	2.00%
Missing	705	10.70%
Length of stay, mean, standard error	6.58	0.14
Discharge Disposition		
Routine	5051	77.00%
Other Health Care Facility	1351	20.60%
Against Medical Advice (AMA)	36	0.50%
Died	126	1.90%
APRDRG_Severity		
Minor loss of function	107	1.60%
Moderate loss of function	1822	27.80%
Major loss of function	3718	56.60%
Extreme loss of function	916	14.00%
Hospital Region		
Northeast	1197	18.20%
Midwest	1755	26.70%
South	2236	34.10%
West	1375	21.00%
Clinical Comorbidities		
Chronic pulmonary disease	1457	22.20%
Coagulopathy	1195	18.20%
Diabetes, uncomplicated	676	10.30%
Hypertension	1204	18.30%
Hypothyroidism	1359	20.70%
Liver disease	140	2.10%

Other neurological disorders	1244	19.00%
Renal failure	358	5.50%
Valvular disease	610	9.30%

Table 2. Variables associated with psychiatric comorbidities in multivariate logistic regression analysis

	Odds ratio (95% confidence interval)	p-value
Age	1.011 (1.007-1.016)	<0.001
Female (reference : Male)	1.17 (1.057-1.295)	0.002
Non-white race (reference : White)	0.662 (0.59-0.743)	<0.001
Severity of illness (reference : Minor loss of function)		
Moderate loss of function	1.324 (0.888-1.973)	0.17
Major loss of function	1.179 (0.795-1.747)	0.41
Extreme loss of function	0.873 (0.578-1.318)	0.52
Discharge Disposition (reference: routine discharge)		
Other healthcare facility	1.28 (1.128-1.453)	<0.001

Against Medical Advice	3.449 (1.647-7.222)	<0.001
Death	0.375 (0.236-0.597)	<0.001
Length of stay, days	1.021 (1.015-1.027)	<0.001

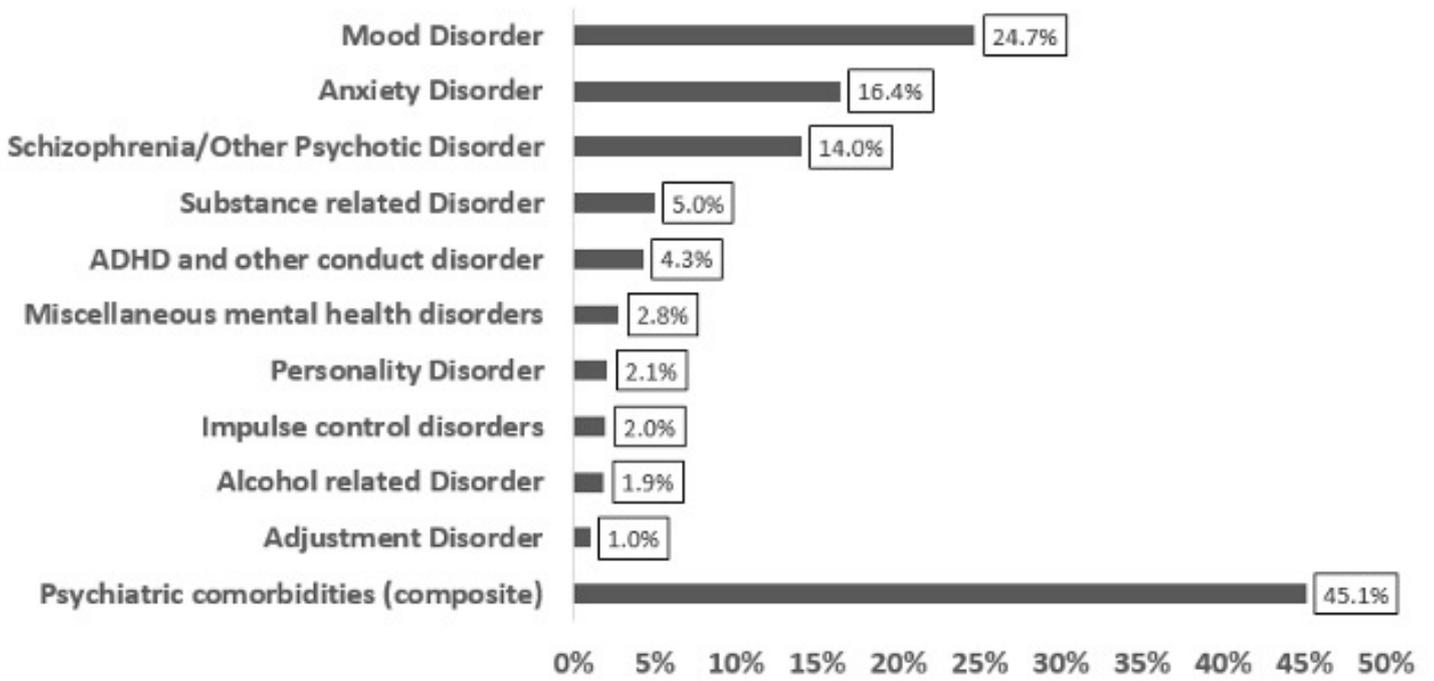


Fig. 1. Figure 1. Psychiatric Comorbidities in patients with DiGeorge Syndrome