

Down Syndrome and Major Depressive Disorder: A Review

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The high prevalence of Psychiatric Disorders in Individuals with Mental Retardation is fairly well established. Individuals with Down syndrome had been conceived in the past as happy and cheerful people and were thought not to suffer from Major Depressive Disorder. There is a relatively limited data on the issue of Major Depressive Disorder and Down syndrome in the literature. However there is a growing body of evidence that individuals with Down syndrome do indeed suffer from Major Depressive disorder. There is no neurobiological basis to suggest that Down syndrome and Major Depressive Disorder may be mutually exclusive. In this paper, we will review the current literature on the Major depressive Disorder in Individuals with Down syndrome and present updates on treatment.

Keywords: bipolar disorder, depression, Down syndrome, ECT, SSRI, suicide

The fact that people with mental retardation (MR) suffer from a high prevalence of psychiatric disorders is fairly well established.^{29,30} The presentation of these disorders may be unusual and at times the process is complicated.^{25,29} Despite earlier disagreement on whether major depressive disorders can be diagnosed in patients with moderate to profound mental retardation, it is fairly well established now, that people with MR suffer from depression.⁴⁴ There have varying reports on the prevalence of depressive disorders in individuals with MR. One report concluded that the prevalence rate is much higher than 0.9% and 5%.³ Some reports have mentioned a figure between 1% and 5%.⁴³ It does seem likely that affective disorders occur at least as commonly in persons with MR as in the normal population.

There is relatively limited data on the topic of depression and Down syndrome. This is surprising as it has been found that depression is three times more likely to occur in people with Down syndrome than in people with learning disabilities of other etiologies.⁶

There is a stereotyped presentation of persons with Down syndrome is as happy and cheerful individuals. There is, however, a growing body of evidence that points to the presence of depressive disorders among individuals with Down syndrome. Children with Down syndrome generally portray a happy countenance and this changes as they grow towards adulthood. A growing number of case reports of major depression in persons with Down syndrome have been published since 1961.²² This paper aims to present a review of the current literature on the subject of major depressive disorder among individuals with Down Syndrome.

EPIDEMIOLOGY

Down syndrome affects people of all ages, races and economic levels. Down syndrome is the most commonly occurring genetic condition. It is the most frequently occurring chromosomal abnormality, occurring once in approximately every 800 to 1,000 live births. Over 350,000 people in the United States alone have Down syndrome. 95% of the cases are due to the presence of an extra chromosome 21. In about 5% of the cases there is translocation defect.¹⁶ Epidemiological studies of psychiatric disorders in children and adolescents with Down syndrome have not shown an increased frequency of depression.^{12,19,20} The evidence in the literature suggests that children and adolescents with Down syndrome are likely to be at lower risk for psychiatric disorders than are children and adolescents with MR of other etiologies. Conversely, it does appear that children and adolescents with Down syndrome are at higher risk than those in the general population.²¹

In studies of adults with Down syndrome, one report did not note any with major depressive disorder among 44 of the subjects with Down syndrome living in the community.¹⁷

Another paper reported major depressive disorder in 10 of 164 (6.1%) individuals with Down syndrome at an outpatient clinic.²⁰ Another report noted depression among 42 of 371 people with Down syndrome and in 16 of 371 matched control adults with MR.⁶ In this report there was no comparison with the general population. It has been noted that, based on the current evidence, adults with Down Syndrome may be at a greater risk for major depression than other adults with MR. This has led to the hypothesis that people with

Down syndrome are at an increased risk of depression because of the extra 21.²¹ It is clear that further research is needed to clarify this issue.

CLINICAL FEATURES

An earlier paper reviewed the subject of mood disorders and Down syndrome and noted that sad affect, social withdrawal, anhedonia, tearfulness, decreased energy, psychomotor retardation, depressed appetite, regression in self-care skills, sleep disturbance, hypochondriasis, aggression/ tantrums, reduced speech, increased dependency and irritability have been described as symptoms of depression among individuals with Down syndrome.²³ In one report, the authors describe the clinical features of twenty-two individuals with Down syndrome and major depressive disorder.²² Their subjects included nine persons with Down syndrome and major depressive disorder followed at an outpatient clinic and thirteen cases of Down syndrome and major depressive disorder reported in the literature. The authors reported that depression is rarely verbalized and commonly appears as tearfulness, sad facies and lability of mood. Vegetative symptoms such as anhedonia, withdrawal, mutism, psychomotor retardation, decreased appetite, weight loss and insomnia were noted to be prominent in their review of the subjects. It should be added that, among all the subjects reported in this study, only one was functioning within the range of mild MR and suicidal ideation, self-depreciation and guilt was also reported for that subject.²² Overall, we conclude it is fairly well established that the presentation of depression among persons with Down syndrome is likely to be dominated by vegetative symptomatology of psychomotor retardation, sleep and appetite disturbance.

Verbal expressions of preoccupations of suicide, death, self-depreciation and guilt have been reported to be uncommon features of the presentation of depression among Down syndrome persons.^{10,22,23} The explanations for these observations are that these symptoms were either not present or were not reported due to mutism or MR. Others have noted in various reports that vegetative symptomatology with few verbal complaints may be related to the level of MR. This explanation is not supported by evidence and it is clear that further research is needed to study the presentation of depression across different levels of MR.

It has been generally accepted that suicide is uncommon among persons with MR. Although there are reports documenting suicidal behavior among individuals with Down syndrome and depression, these are few

in numbers. One report found a rate of nine suicide attempts per 1000 individuals with MR.³⁵

Another report examined 90 consecutive admissions to an inpatient service for children and adolescents with MR and found ten persons who showed suicidal behavior and 60% of these acts were considered to be potentially lethal.⁴⁰ Another study reported on 12 persons with MR who had made a suicide attempt.² One report has documented an act of suicide.⁴ Overall, this low rate of suicide has been attributed to several factors linked to cognitive impairment, such as lack of ability to make cognitive connections between the feelings of depression and thoughts to end one's life. Also, limited planning ability and lack of opportunity because of supervision by family or staff have been cited as explanations. Recently, there has been further documentation of suicide attempts among individuals with MR. A report describes two cases of major depressive disorder in persons with Down syndrome.(13) Both cases articulated their feelings and carried out acts which were potentially lethal. Both of these individuals with Down syndrome functioned in the mild range of MR. This suggests that in Down syndrome individuals with mild MR with an ability to articulate their feelings and thoughts, verbal symptoms such as suicidal ideation, guilt and self-depreciation can be common, and it would be reasonable for mental health practitioners to screen for these symptoms. This would assume significance if one considers that although impaired intellectual ability and poor planning skills may limit the success of plans for suicide, a majority of suicidal acts are impulsive and are acted on without any significant planning.¹³

Literature notes that hallucinations are frequently reported among individuals with Down syndrome and depression.^{23,41} In one report, hallucinations were noted to be occurring in 10 of the 22 persons with Down syndrome and major depressive disorder. This association could be related to the level of MR. It is possible that the higher prevalence of hallucinations may be peculiar to major depressive disorder and Down syndrome and another possibility is that psychotic depression is prominent in this population. It is hoped that further investigation will shed some light on this issue.

In one report, 21 of the subjects presented with five or more Down syndrome DSM-III-R criteria.¹ It was noted that more vegetative symptoms were more common.²² Another report noted that among 378 adults with Down syndrome, 42 individuals were identified to have experienced one episode of depression. A total of 56 episodes were reported for these 42

individuals. Twenty-eight of these episodes met DSM-III-R criteria and 38 episodes met criteria.^{1,43} A mean age of onset of depression was reported to be to be 30.1 years of age, and consistent with what has been noted above, more biological symptoms were noted to be the present.¹⁰ It does appear that the presenting psychopathology of major depressive disorder in persons with Down syndrome is similar to major depressive disorder as defined in DSM-III-R. It should be pointed out that the interpretation of the presence or absence of subjective symptoms in a population with limited verbal skills is a challenge. A proposal has been that DSM criteria be adapted with a greater emphasis on vegetative symptoms and relatively less attention be given to verbal symptoms.³² To facilitate the process of assessment and diagnosis, modified DSM symptoms have been utilized in the studies examining this population, especially in cases where functioning has been in the range of severe and profound MR.

A more recent comprehensive study,²⁴ which is the first population survey of suicide behavior in persons with Down syndrome, compared suicidal behavior among persons with Down syndrome to a control population of persons who MR had other etiologies. Among 11,277 persons with Down syndrome, 4 (0.04%) had suicidal behavior in the previous year, compared to 1.142 (0.8%) of 143, 143 individuals in the control group. The difference is highly significant because this suggests that a person with MR without Down syndrome is ten times as likely to show suicidal behavior as a person with Down syndrome. In the same study, the rate of depressive-like behavior in Down syndrome was 2.3% whereas it was 7.1% in the control group of persons whose MR had other etiologies. Another important finding in that study is that attempted suicide was significantly more likely if the person had epilepsy than those without epilepsy if age, MR level, bipolar affective disorder and absence of Down syndrome were controlled. Although other studies have detected an increase in depression among persons with Down syndrome, this study did not which made the authors to raise the possibility that perhaps the instrument used (i.e., Client Development Evaluation Report) was not sensitive enough. However the validity and reliability of this instrument has been reported. Other possibilities include the presence of depressive-like behaviors among individuals with Down syndrome due to dementia or some other conditions or perhaps the previous studies have over estimated depressive illness in persons with Down syndrome.

Another recent report looked at immune function during depression in individuals with Down syndrome and examined depressed and

non-depressed individuals with Down syndrome with intellectual disability. The statistically significant findings in their study replicated the findings in depressed subjects without Down syndrome and intellectual disability. The results imply that certain immune responses and macroglobulin elevations can serve as markers of depression. This probably assumes greater significance for the MR field than for the non-MR field. The ability to improve accuracy of diagnosis through the help of a laboratory test in a difficulty to diagnose population, while be extremely important in helping clinicians to use appropriate psychotherapeutic techniques and medications.³⁸ It is hoped that further research will probe this issue and will help clarify it.

Sovner and Hurley,³⁴ in a 1993 commentary, had proposed a new term, "psychotoform" psychopathology, which describe fantasies and beliefs in individuals with Down syndrome. This is to acknowledge the unusual nature of the beliefs or behavior in question without prejudging whether they reflect psychotic process or represent an adaptive developmental function. The symptoms and signs that are proposed to be included the following:

1. talking to oneself;
2. acting out "mini dramas" that involve many different persons and the individuals playing all of the roles;
3. fantasies and reveries that have a delusional-like quality, especially those with a grandiose or erotomanic content;
4. bizarre behavior e.g. smearing feces;
5. preoccupation with specific objects;
6. severe ritualistic behavior;
7. the experiences associated with posttraumatic stress disorder.

It is hope that further research will investigate the presentation of psychotic and "psychotoform" symptomatology in the MR population.

DIFFERENTIAL DIAGNOSIS

The diagnosis of major depressive disorder is challenging in individuals with Down syndrome because their intellectual deficits limit the extent to which they can convey and express their inner mental life, limiting identification of psychopathology. The limited ability of these individuals to verbalize psychiatric symptoms and certain conditions mimicking affective symptomatology increase the the *diagnostic overshadowing* within the field. In spite of the difficulties, an attempt to make a clear and accurate diagnosis is possible if approached in the correct manner.

There are certain conditions that Alzheimer's dementia is very likely to mimic the presentation of depression in these individuals.²³ The difficulty of neuropsychological and memory testing of cognitive functions in patients who have MR and individuals who are quiet, withdrawn and non-complaint has been reported.²² On the other hand, the cognitive and behavioral deterioration with a pronounced change in affect associated with depression in individuals with Down syndrome can be mistaken for Alzheimer's disease.⁴¹ One report notes that affective disorders be considered in the differential diagnosis of dementia in individuals with Down syndrome, especially in those under 35, those with a clear evidence of memory impairment, those with fluctuating and episodic evidence of behavioral regression, those with a pronounced change of affect along with a decline of vegetative function and those with prominent delusions and hallucinations⁴¹

A very detailed account of the differential diagnosis of clinical symptoms of depression appears in a paper by Pary *et al.*²³ in 1996. That report notes complicated and uncomplicated grief as probable etiologies etiologies mistaken for depression. A recommendation arising out of clinical experience is to rule out depression if the grief reaction is not limited to a couple of months. Among medical conditions are listed sleep apnea, tooth abscess, seasonal allergic rhinitis, and secondary infections as likely causes of vegetative symptoms such as sleep disturbance and lack of appetite. Individuals with Down syndrome are more susceptible to develop infections of the ears, sinuses, airways and lungs.²³ In addition, approximately 50% of individuals with Down syndrome may have sleep apnea.³¹ A retrospective chart review investigating the occurrence of headache among individuals with MR and developmental disabilities diagnosed with affective illness found a higher reported incidence of headaches among those diagnosed with affective illness.²⁷

Hypothyroidism can cause a decline in functioning and present with symptoms and signs similar to major depression such as mental slowing. Thyroid disease is common in Down syndrome. Dinani and Carpenter.¹¹ found that of 106 adults with Down syndrome, 43 (40.5%) had abnormal thyroid function, and over 60% were 35 years of age or older. Another study, however, did not find an increased prevalence of hypothyroidism in individuals with Down Syndrome and depression.⁶ Another report investigated the association of depression in Down syndrome individuals with thyroid status and no statistically significant association between

depression and thyroid dysfunction was found.¹ It is very important that hypothyroidism be ruled out in all individuals with Down syndrome showing signs and symptoms of major depressive disorder.

Among psychiatric illnesses known to occur among individuals with Down syndrome are adjustment disorders, anorexia nervosa, and other eating disorders, anxiety disorders, autistic disorders, disruptive behavior disorders such as attention-deficit hyperactivity disorder, conduct and oppositional behavior disorders, elimination disorders, paraphilias, repetitive behaviors such as Tourette's syndrome, tic disorders, stereotypic disorders, self-injurious behaviors, and lastly, schizophrenia and other psychosis.²¹ Sometimes, the features of these disorders may contribute to the clinical presentation and it would be pertinent to distinguish between these disorders. The available literature has noted the high frequency of psychotic features in individuals with Down syndrome. These psychotic symptoms may not have any significance or could be a part of other psychiatric illness such as posttraumatic stress disorder, autistic disorder, or obsessive-compulsive disorder.²³ Since the original description of mania among individuals with Down syndrome, others have documented the compatibility of Down syndrome with bipolar disorder, it would be pertinent to include bipolar disorder in the differential diagnosis of a Down syndrome individual presenting with depression.^{7,18,26} Among psychiatric disorders, so far not reported among individuals with Down syndrome, are personality disorders and substance use related disorders.²¹

CO-MORBIDITY

Among individuals with Down syndrome, the issue of co-morbidity has not received much attention. One report found overlap in the presentation of depression and dementia in individuals with Down syndrome and this was not reported in the control group.³ This association has been offered as an explanation for the observed increased vulnerability of individuals with Down syndrome to develop depression. In the general population with Alzheimer's dementia, the development of dementia may be preceded by depressive symptoms. Though the fact that the mean age of onset of depression in individuals with Down syndrome is about 30 years and the mean age of onset of dementia is about 54 years, suggests that this is an unlikely explanation.

One report has described a case of anorexia and mood disorder in an individual with Down syndrome.³⁷ Another report documented the presence of anorexia nervosa, major

depression and obsessive-compulsive disorder in a Down syndrome individual. This individual functioned within moderate MR range and the authors speculated on the possibility of his developing Alzheimer's disease because of untreated major depression and obsessive-compulsive disorder.

TREATMENT

It is difficult to recognize and diagnose depression in individuals with Down syndrome. Once an accurate diagnosis is established, however, treatment attempts should be initiated as soon as possible. The quality of life of a person with Down syndrome is impaired and with treatment they can regain their pre-morbid functioning.³⁶

Among non-pharmacological interventions, cognitive-behavioral techniques ought to be attempted if the individual is able to verbalize their feelings and thoughts relevant to their situation. Likewise, group therapeutic approaches can be beneficial in situations involving psychosocial aspects of having a major depressive disorder. The ability of an individual with intellectual disability to respond to psychotherapy is not closely related to their IQ and is rather more relevant to the individual's ability to relate to their therapist.²³

In appropriate circumstances the utility of psychotherapeutic approaches ought to be kept in mind. Dysarthria makes some verbal therapies difficult in persons with Down syndrome. Persons with mild MR may be able to write about feelings and thoughts.

The psychopharmacological treatment guidelines are generally the same as for any patient with depression. Serotonin level abnormalities have been documented among individuals with Down syndrome.³⁹ Serotonergic medications may be more effective than other medications.²¹ One report noted that 20 of 22 Down syndrome subjects with depression responded to treatment. Out of the responders, 17 responded to antidepressants. Of these seventeen, 11 responded to serotonergic agents and 6 responded to amitriptyline, which is partially serotonergic. Non-response was noted for desipramine, which is noradrenergic.²² Generally, treatment with either a tricyclic antidepressant (TCA) or specific serotonin reuptake inhibitors (SSRI's) should be initiated and used according to the usual guidelines.^{14,23}

Among treatment resistant cases, first, the diagnosis and prior treatment adequacy ought to be reconsidered. After addressing these issues, another antidepressant can be considered. If the patient is non-responsive after a series of trials, augmentation strategies ought to be considered. The use of thyroid

hormone should be tried as a first line augmentation strategy. Also, lithium carbonate and anticonvulsants such as valproate and carbamazepine are other available agents although Lithium may not augment SSRI as well as it will for the heterocyclics. Another approach can be the careful use of multiple antidepressants.²³

There are reports in the literature documenting the use of electroconvulsive therapy (ECT) for the treatment of depression in persons with Down syndrome. Three cases responded to the use of ECT.⁴¹ Another report mentioned the use of ECT in persons with Down syndrome and depression.¹⁵ A review of ECT use for persons with developmental disabilities notes that there are 14 reports describing ECT treatment of 20 individuals with intellectual disability. A case of recurrent psychotic depression, which responded to acute and maintenance ECT is also described. Considering the high frequency of occurrence of psychotic features among Down syndrome persons with depression, the use of ECT can be considered in someone with a diagnosis of psychotic depression who has not responded to other available treatment strategies.

PROGNOSIS

Little has been reported on the long-term prognosis of depression in people with Down syndrome. One report looked at short-term prognosis of depression in Down syndrome persons. For individuals with depression, adaptive functioning was lower compared to maladaptive functioning. At one-year follow up, a majority of the Down syndrome individuals with depression were symptomatic although some improvement was noted. Short-term prognosis appeared to be possibly better the earlier the age of onset of depression. A mean age of onset of depression was noted to be around 30 years.²⁸

Individuals with Down syndrome and a past history of depression function less well in terms of adaptive behavior than those with no past psychiatric history.⁵ In terms of adaptive behavior, people with Down syndrome and a past history of depression perform at a higher level the older their age at the first episode of depression and perform at a lower level if their age at the first onset of depression is earlier. One implication is that people of lower ability become depressed earlier and if that were to be the case, then individuals with a lower ability would be at a higher risk for recurrences.⁸ To the contrary, the relapse of depression has been associated with a later age of first onset when compared with a single episode of depression and it is unlikely that the above implication is correct.⁸ Follow-up studies have

found relapse of depression to be associated with short duration of episodes, absence of associated life events prior to the first episode and the presence of biological symptoms of depression.⁹

The differing prognosis can be explained in terms of acquisition of skills and confidence level of a particular individual. The older the individual, the more skill they achieve. The impairment in skills and confidence with an episode of depression may have more deleterious effects on a younger person than an older person.

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