Open Journal of
Clinical & Medical
Case Reports

Volume 7 (2021)
Issue 01

ISSN: 2379-1039

Down's syndrome disintegrative disorder: When young people with down's syndrome regress. A case report

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Abstract

Mr X has Down's syndrome. He was referred to the Community Learning Disability Team at the age of 22 with one year's history of cognitive deterioration. He became increasingly confused and forgetful, with a significant impact on his daily functioning and subsequently his quality of life.

Serial cognitive assessments showed an initial deterioration which did not persist, and in fact eventually showed an improvement compared to the baseline assessments, some two and a half years after the initial referral.

Mr X was diagnosed with Down's Syndrome Disintegrative Disorder (DSDD), a condition which is being increasingly reported in the literature. Due to similarities in presentation, it can be mistaken for Alzheimer's dementia, however prognosis and treatment of the two conditions are different. Consequently, it is important for physicians to identify DSDD, ensuring timely diagnosis and that appropriate discussions are had with the patient and their carers regarding likely prognosis.

Abbreviations

DSDD: Down's syndrome disintegrative disorder; APP: Amyloid precursor protein; CLDT: Community learning disability team; CT: Computerised tomography; MRI: Magnetic resonance imaging; DLD: Dementia questionnaire for people with learning disabilities.

Background

Down's Syndrome (Trisomy 21) is a common genetic cause of intellectual disability as well as being a common chromosomal disorder. With a prevalence of approximately 1 in 350 births in England per year [1], there are around 40,000 people in the UK living with this syndrome [2]. Down's Syndrome is associated with a number of co-morbidities including congenital heart disease, sensory impairment, hypothyroidism,

acute lymphoblastic leukaemia and Alzheimer's dementia.

There have been reports within the literature of a condition in people with Down's Syndrome that encompasses cognitive decline with associated loss of skills, including loss of speech. This presentation usually happens at a young age (10-30) and often is not progressive, with some degree of recovery possible. This phenomenon has been variously termed Young Adults with a Disintegrative Syndrome [3], Catatonic Psychosis [4], Catatonia in Down's Syndrome [5] and Acute Regression of Down's Syndrome [6] . The more commonly used term, Down's Syndrome Disintegrative Disorder (DSDD), is used by Worley et al in 2015 [7].

Due to the nature of the presentation of this condition, it is not uncommon for a diagnosis of Alzheimer's dementia to be considered. Estimates suggest up to 50% of people with Down's Syndrome will develop Alzheimer's dementia [8], with the increased prevalence suspected to be due, at least in part, to the location of the Amyloid Precursor Protein (APP) gene on chromosome 21.

There are key differences between DSDD and Alzheimer's dementia. DSDD usually presents at a younger age, it is rare, even for someone with Down's Syndrome, to develop signs of Alzheimer's dementia before the age of 35 [9]. People with DSDD can recover from the regression, which isn't possible in Alzheimer's dementia. DSDD is also associated with other signs including autistic features and thyroid autoimmunity [7].

DSDD is an under-recognised condition which could be potentially misdiagnosed as Alzheimer's dementia. This could lead to inappropriate treatment with acetylcholinesterase inhibitors as well as having a psychosocial impact on patients and families being given incorrect diagnoses and prognoses.

Case Presentation

Mr X was first seen by the Community Learning Disability Team (CLDT) in 2016 at the age of 22. He had diagnoses of Down's Syndrome, Mild Learning Disability, Cardiomyopathy and sensory impairments (both visual and auditory). He had been referred to the CLDT by neurology having had an appointment due to concerns around increasing confusion and tremor. Neurology had ruled out Parkinson's Disease, but suggested a likely diagnosis of Alzheimer's dementia. Mr X was then referred to the CLDT for further assessment of his cognitive deterioration.

On initial assessment by both nursing and psychiatry, a number of symptoms were identified that had developed over the previous year. These included increasing confusion, which resulted in him no longer completing a number of activities of daily living which he had previously performed independently. He also developed incontinence, word finding difficulties, social withdrawal, anhedonia and increasing anxiety.

There was no clinical evidence at initial assessment of any other mental illness and the absence of biological symptoms of depression ruled out the possibility of pseudo dementia associated with depression.

At this point there was uncertainty around the diagnosis, although neurology's diagnosis of Alzheimer's dementia was considered. A previous CT head had shown potential temporal lobe atrophy, and an MRI head was awaited. Following information provided from Mr X's family, it was agreed by the multidisciplinary memory team that his diagnosis was consistent with moderate dementia, despite his young age, and he was commenced on memantine (a glutamate receptor antagonist licenced for the treatment of moderate to severe dementia in Alzheimer's disease). This was three months after his initial psychiatry appointment and medication was only commenced after extensive discussion with Mr X and his family regarding the risks and benefits of memantine therapy.

Five months after being commenced on memantine, his MRI head was found to be normal, with no evidence of atrophy. Nursing staff had completed a 'Dementia Questionnaire for People with Learning Disabilities' (DLD) at the point of first referral and subsequently 6 months later. This is a validated screening tool which is based on carer observations. It provides scores in a number of areas, divided into cognitive and social, with higher scores representing poorer performance. Although not diagnostic, it is a useful tool for monitoring progression of deterioration and response to treatment. Mr X's scores showed a deterioration in both cognitive and social domains over the initial 6 month period, which suggested limited benefit from the memantine therapy.

At this point, especially due to Mr X's age and the absence of atrophy on the MRI scan, the diagnosis of Alzheimer's dementia was reviewed, and DSDD was considered. In the literature an association between DSDD and raised thyroid peroxidase antibody levels has been identified so at this point thyroid peroxidase antibody titres were checked, however these came back within normal limits.

Mr X's antidepressant, citalopram, which had been commenced at initial assessment by the neurologist was gradually discontinued, which led to some slight improvement in his presentation. He remained on memantine therapy following discussion with Mr X and his family who feared a further deterioration if the memantine were discontinued. His family continued to report his presentation as being variable, at times he appeared to be deteriorating, but at other times less so.

Two years after his initial referral, his ongoing psychology assessment was completed. He had undergone a serial battery of cognitive assessments across three time periods with no significant change in his score. Carer assessments however suggested ongoing decline, which was not evidenced in the cognitive assessments.

In the background throughout this time, Mr X experienced a number of physical health problems which may have impacted on his presentation. These included an arterial clot in his leg which required surgery and ongoing heparin injections. He also experienced sub-acute bowel obstruction.

Mr X was seen in a joint psychiatry and neurology clinic where he was noted on examination to have palmar reflex and grasp reflex which was felt to fit with his deterioration in cognitive functioning.

He was reviewed again in clinic, three years after his initial referral. His DLD scores were better than

at the time of referral. His memantine was discontinued due to consistently elevated liver enzymes. The discontinuation of memantine did not affect his presentation, which continued to improve.

On review a year later, his cognitive functioning and skills had returned to pre-morbid levels, which provided further evidence for the diagnosis of DSDD rather than Alzheimer's dementia. At the time of writing, Mr X remains well and is functioning normally.

Discussion

This case highlights the importance of keeping an open mind when considering differential diagnoses. It is easy to see someone with Down's Syndrome presenting with confusion and memory impairment and to assume a diagnosis of Alzheimer's dementia. There is less awareness of DSDD among many physicians, however it is a condition that is being recognised more frequently and is clearly an important differential diagnosis to consider in such cases.

It is also important to rule out other potential differential diagnoses including depression and catatonia, both of which may mimic the presentation of DSDD. As such, DSDD could almost be considered a diagnosis of exclusion.

In the case of Mr X, the factors that indicated DSDD as the diagnosis were his young age and the fact that over time his presentation improved. The lack of response to memantine also provided some potential indication, however it is not unusual for people with Alzheimer's dementia and Down's syndrome to have limited benefit from memantine [10].

The association of DSDD with thyroid peroxidase antibody levels has been shown in certain studies, with Worley et al showing raised titres in 91% of DSDD cases compared to 23% of control cases [7]. Interestingly in that study, the one case that was not positive for thyroid peroxidase antibodies did develop anti-TSH antibodies, meaning 100% of cases had thyroid autoimmune disease of some sort. In this study the rates of raised thyroid peroxidase antibodies was higher than in other reported studies, where other figures were nearer 38% [11,12]. Hashimoto encephalopathy, "a syndrome of persisting neurological and neuropsycholgical deficits with elevated titres of antithyroid antibodies"[7] has been described in Down Syndrome [13] , and potentially this could represent a link between DSDD and Hashimoto Encephalopathy. This requires further research.

Key Points

1. Down's Syndrome Disintegrative Disorder presents with cognitive decline with loss of skills at a young age.

2. Important differentials to rule out prior to giving a diagnosis of DSDD include Alzheimer's Dementia and depression.

3. Key discriminating features in DSDD include the early age at onset and the reversible nature of the dete-

rioration.

4. DSDD is an important diagnosis to identify to ensure appropriate discussion with patients and families regarding prognosis and management options.

Consent: Informed consent was obtained from Mr X and his family for this anonymised account of his experience.

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Manuscript Information: Received: August 12, 2020; Accepted: January 26, 2021; Published: January 30, 2021

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Citation: Howe G, Bright C. Down's syndrome disintegrative disorder: when young people with down's syndrome regress. A case report. Open J Clin Med Case Rep. 2021; 1725.

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