Genetic abnormalities in catatonia: a systematic review

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Introduction

- Catatonia is a severe neuropsychiatric disorder that can occur in the context of a range of psychiatric and general medical disorders[1].
- The major psychiatric diagnostic manuals (ICD-11 and DSM-5-TR) have now recognised that catatonia is not necessarily part of schizophrenia.
- There are many potential aetiologies underlying catatonia and despite extensive investigation, there remains a proportion of patients, for whom no clear cause is identified[2].
- Twin studies of psychiatric disorders in the 20th century subsequently confirmed these disorders had a heritable component[3].
- Modern psychiatric genetics research has advanced our understanding of psychiatric disorders. Genome wide association studies have endeavoured to identify specific genetic variants however they account for only a small proportion of the heritability estimated from twin studies[4].

Aim

- There is increasing interest in the genetics of catatonia.
- Making a genetic diagnosis in catatonia could be important for ascertaining prognosis, guiding investigations for other features of a particular syndrome and for certain conditions accessing disease-modifying therapies.
- Currently, however, no comprehensive synthesis of genetic abnormalities in catatonia exists in the published literature.
- We aimed to conduct a systematic review to identify the genetic abnormalities reported in catatonia, their frequency and - where possible - the strength of any association.
- Due to the anticipated heterogeneity of the literature, we planned to conduct a narrative synthesis without meta-analysis.

Methods

- In this systematic review (PROSPERO CRD42023455118) we searched MEDLINE All, Embase classic + Embase, PsycINFO and AMED up to 15/08/23.
- Eligibility was initially screened by title and abstract by two authors (KR & IC) independently with blinding using the Covidence software. The same procedure was used to evaluate full texts.
- Data were extracted independently with blinding from eligible full-text articles by a group of authors (IC, KR, JBF, JB, ER. BC, CW). Where discrepancies occurred between the two original extractors, a third author arbitrated.
- Risk of bias was assessed using the Joanna Briggs Institute quality assessment tools. Risk of bias was categorised as low, moderate or high risk.

	Inclusion	Exclusion
Population	All age groups with testing for a genetic disorder (or alternative means of identifying a genetic disorder, such as biochemical testing) and phenotyping for catatonia	Animal studies
		Studies that did not formally assess participants for catatonia or genetic disorders
Exposure	Genetic disorder, copy number variants (CNV) (including all degrees of penetrance)	No genetic disorder described.
Comparison	Participants without catatonia who had the genetic disorder, OR	-
	Participants with catatonia who did not have a genetic disorder.	
Outcome	Description of catatonic clinical features without specified diagnostic criteria, OR	-
	Catatonic clinical features without a definitive diagnosis, OR	
	Catatonia defined by DSM-IV, DSM-5, ICD-10 or ICD-11	
Study design	Published original research available in English or French, AND	Studies that are not original literature (e.g. systematic reviews, scoping reviews, and protocols)
	Peer reviewed or non-peer reviewed, AND	
	Case reports, case series, cross-sectional studies, case-control studies or cohort studies, AND	
	Journal articles, conference abstracts or conference proceedings.	

Table !. Inclusion and exclusion criteria

Results

- We extracted data from 99 eligible studies, 54 of which were case reports
- Of 8600 included individuals, 636 had both catatonia and a genetic abnormality. Sex was reported for 6080 individuals, of whom 3208 (52.8%) were male.
- Mean age at onset of catatonia was 28.8 years (SD 16.3). The median duration of the index catatonic episode was 180 days (IQR 38 to 668).
- Course of illness was complicated by more than one episode of catatonia in 28.1% of the population.
- We did not identify a profile of catatonic features that can clearly distinguish a genetic aetiology across the lifespan. Stupor and mutism were the most frequently reported symptoms (Figure 1).
- A wide range of genetic conditions were reported in catatonia, including Phelan-McDermid syndrome (n=80), 22q11.2 deletion syndrome (23), Down's syndrome (19), Cornelia de Lange syndrome (9), fragile X syndrome (6), Marfan's syndrome (6) and Wilson's disease (3), as well as 41 other conditions with only 1 or 2 cases.
- Psychosocial stressors were commonly identified as precipitants for catatonic episodes. Study quality was good in 29 studies, moderate in 53 and poor in 17.
- The major focus of association studies has centered on periodic catatonia; despite identifying candidate genes at both 22q13 and 15q15, none have been replicated.

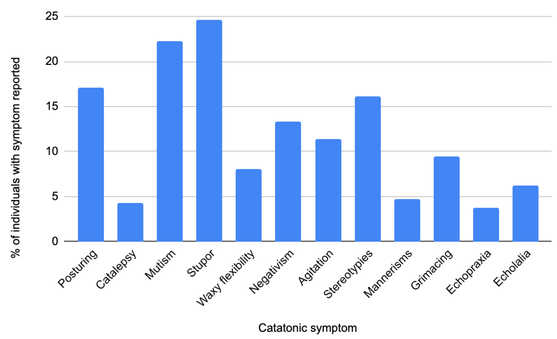

Figure 1: Bar chart showing catatonic signs present in individuals with catatonia and a genetic condition

Discussion

- Many case reports in this review described psychosocial precipitants. Patients with genetic syndromes associated with learning difficulties may therefore be particularly vulnerable to developing catatonia as a stress response.
- It remains to be seen whether the genetic variants associated with catatonic schizophrenia will be the same as catatonia of all causes
- This work is limited by the quality of the data used which comprised mostly case reports which are vulnerable to incomplete reporting of case histories and limited length of follow-up for key outcomes.
- Reporting of genetic testing methods was also incomplete across all study designs.
- Discrepancies between association studies could be attributed to the use of the Leonhard (1999) system, which does not align with the ICD-10

Conclusion

- Whilst specific syndromes such as Down's syndrome, DiGeorge syndrome and Phelan-McDermid syndrome have been frequently associated, our data show catatonia can occur in a wide range of genetic abnormalities.
- Understanding these genetic risk factors may reduce the risk of developing catatonia through early modification of precipitating psychosocial stressors

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