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Psychological aspects of genetic counselling in rare genetic CNS disorders - should regulators play a greater role?

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BACKGROUND

Genetic disorders may either be inherited from one or both parents or appear as spontaneous mutations or chromosomal changes. The diagnosis of a rare genetic disease is based on the presence of clinical symptoms and on examinations such as tissue biopsy, anatomical and functional neuroimaging, and laboratory tests that may be useful in differential diagnosis.

In the US, a disease is classified as rare when it affects fewer than 200,000, while the European Commission has defined this threshold at less than 5 cases per 10,000 people.

The use of genetic testing is becoming increasingly popular due to technological advances and intensified patients' interest in knowing their genetic status.

As a result, medical quidelines may recomment genetic testing for patients who have a first-degree or second-degree relative with the disease. Increasingly, asymptomatic individuals want to know the risk of developing the disease, even if they have no family history of the condition. There are no regulatory requirements on the provision of psychological counselling along with genetic counselling.

OBJECTIVES

We sought to review rare genetic CNS disorders subject to genetic testing and discuss the need for and practical aspects of psychological counselling for people diagnosed with disease-associated gene variants.

METHODS

Literature review.

RESULTS

Major rare genetic CNS disorders subject to genetic testing

- **Amyotrophic lateral sclerosis (ALS)** is a fatal neurodegenerative disorder and is the most common type of motor neurone disease (MND). ALS is an adult-onset disease, presenting with the loss of upper and lower motor neurons as a result of progressive muscle weakness and paralysis; 20–50% of affected patients develop cognitive dysfunction, and 5–15% develop dementia. Ninety to 95% of reported cases of ALS have no defined genetic basis and are considered as a sporadic form of ALS (sALS). The remaining 5–10% have at least one other family member affected, and are classified as familial ALS (fALS).
- **Huntington's disease (HD)** is a neurodegenerative disorder that typically starts at the age of 45 years. Symptoms include chorea, motor and cognitive impairment, and dementia. HD is caused by the presence of an expanded CAG trinucleotide repeat in a gene on chromosome 4p16.3.
- **Duchenne muscular dystrophy (DMD)** is a neuromuscular disorder affecting males. DMD symptoms appear in early childhood, resulting in disability by the age of 12 years and premature death due to cardiorespiratory complications by the age of 20. Intellectual disability is also characteristic of DMD; common symptoms include motor delay, gait abnormalities, difficulty rising from the ground, and frequent falls. DMD is caused by mutations in the dystrophin gene located at Xp21.

Impact of the genetic background of rare diseases on genetic counselling

- Rare genetic disorders include a heterogeneous group of diseases with a wide range of clinical symptoms resulting from gene mutations or chromosomal aberrations. For most disorders, curative treatments have not been developed and remain in the experimental phase.
- In illnesses such as HD, in which a **direct association** between a number of CAG repeats and clinical presentation occurs, genetic counsellors can offer reliable information on the course of the disease.
- In diseases with a more **complex genetic background**, predicting the course of the disease is difficult. ALS is a complex disease belonging to this group. Genetic counselling in ALS is difficult due to allelic heterogeneity that is responsible for the same clinical presentation in different mutations. Genes that are suspected to play a role in the pathogenesis of ALS are often pleiotropic, resulting in a wide range of clinical presentations associated with the same genetic mutation.

Demand for genetic testing of rare CNS diseases

- Despite the **lack of curative and preventive options** and the complexities of most rare genetic disorders, the demand for genetic testing in asymptomatic at-risk individuals is important (1).
- **Asymptomatic individuals** decide to participate in genetic testing because they want to know the risk of developing the disease and to reduce the level of uncertainty (2).
- The main reason identified for foregoing genetic testing is the **difficulty of accepting a positive result, with the lack of curative therapies** and potential negative effects on familial relationships as also important.

Modes and types of genetic testing and counselling

- **Presymptomatic testing** is offered to family members who may be at risk of developing a genetic disease, but do not present any symptoms at the moment of testing. The most common schedules include **pre-decision, pre-test, post-test, and ad hoc counselling (3).**
- There are **ethical concerns** over offering predictive testing to asymptomatic patients with no family history of diseases, such as ALS, where penetrance varies among families. The information about genetic status may lead to significant worry for the individual and the family about the possible development of the disease in the future.
- Additionally, risk data is often estimated based on data from families affected by the condition and the **risk for individuals without family history is unknown**, even if they are carriers of the pathogenic gene variant. Therefore, genetic testing of such individuals is ethically questionable.

Psychological aspects of genetic counselling

- Genetic testing poses a psychological burden on people from families with serious incurable genetic diseases. Patients newly diagnosed with a predisposition to developing rare late-onset genetic disorders may **express a wish to die, have depression, and experience cognitive or behavioral impairment**. More sensitive people with anxiety and those who tend to catastrophise will require psychological support. Assessment of psychosocial readiness before testing may help to plan genetic counselling (3).
- Genetic counselling can result in **physiological and mindset changes consistent with patients' perceived risk profile**. In a study in older adults on the increased genetic risk of developing Alzheimer disease, participants who received information about carrying the pathogenic genotype evaluated their memory more negatively and **performed worse on an objective verbal memory test** than participants with the same genetic status who did not know their genetic status (4).
- Since **merely learning about genetic risk can increase the actual risk**, it remains questionable in what circumstances revealing genetic information is ethical and warranted. In the field of rare CNS disorders that are often not preventable or curable, this **genetic information can rarely be used by patients in a constructive manner.**
- Therefore, the counselors should be able to convey genetic information in a way that **prevents the negative mindset formation**
- For instance, **cognitive behaviour therapy (CBT)** can help mutation carriers identify and challenge "distorted thoughts" and "irrational beliefs" about the diagnoses, which may be contributing to their distress and hindering the adaptation process. They can involve catastrophising ("I will certainly become ill," "I will die prematurely,") and **can contribute to negative mindset formation (5).**
- CBT aims at identifying and articulating thoughts that can lead to negative emotions and at subsequently replacing them with more adaptive thoughts that seem convincing and rational to the patient.
- Currently, genetic counsellors do not undergo specialised training in CBT or psychological counselling.

Implications for the regulators of genetic testing

- It is concerning that the current regulatory requirements for commercial genetic testing **do not involve psychological counselling and do not address the issue of negative mindset formation** which can increase the actual risk of developing the disease.
- The regulatory approval of genetic testing may need to be expanded to ascertain that individuals for whom the risk cannot be estimated are not tested.
- The industry should be encouraged to **develop counseling strategies that can mitigate the negative psychological effects of genetic testing** using their technologies.

CONCLUSIONS

The regulators who approve commercial genetic testing should consider the following patient's challenges:

- Increasingly, asymptomatic individuals want to know the risk of developing the disease. However, revealing genetic risk information to patients can also contribute to negative mindset formation which may, in turn, increase the actual disease risk.
- There are no preventive measures available to asymptomatic people who tested posisitve for rare CNS diseases, therefore the utility of such testing is limtied.
- Psychological counselling that minimises the negative mindset formation should be offered to people who tested positive for pathogenic gene variants.
- The disease risk data is estimated for individuals with family history of the disease and the risk for people withouth family history is unknown. Therefore, testing should only be available to people with family history of the condition.

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