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Genetic testing in intellectual disability psychiatry:

opinions and practices of UK child and ID psychiatrists

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Abstract

Background

An increasing number of genetic causes of intellectual disabilities (ID) are identifiable by clinical genetic testing, offering the prospect of bespoke patient management. However little is known about the practices of psychiatrists and their views on genetic testing.

Method

We undertook an online survey of 215 psychiatrists, who were contacted via the Royal College of Psychiatrist's Child and Adolescent and Intellectual Disability Psychiatry mailing lists.

Results

In comparison to child and adolescent psychiatrists, ID psychiatrists ordered more genetic tests, referred more patients to genetic services, and were overall more confident in the genetic testing process. Respondents tended to agree that genetic diagnoses can help patient management, however management changes were infrequently found in clinical practice.

Conclusions

Differences are apparent in the existing views and practices of child and adolescent and ID psychiatrists. Developing training and collaboration with colleagues working in genetic services could help to reduce discrepancies and improve clinical practice.

Introduction

Approximately 1% of the population has a diagnosis of intellectual disability (ID), which is characterised by impairments in both intellectual and adaptive functioning and has its origin in the developmental period. ID is an aetiologically heterogeneous disorder, with both environmental and genetic causes. Rapid advances in genomics have resulted in many new genetic causes of ID being delineated (Gilissen et al., 2014). Perhaps the better recognised genetic causes of ID occur when individuals exhibit a constellation of symptoms indicative of a known syndrome. In such instances a specific genetic test may be indicated, for example single gene testing in Fragile X syndrome. However, where the individual's presentation is not clearly suggestive of a specific syndrome, chromosomal microarray analysis (CMA) is now typically considered the first line genetic investigation (Miller et al., 2010).

CMA can identify small losses and gains of genetic material. These losses (deletions) and gains (duplications) are referred to as copy number variations (CNVs). Loss or gain of genetic material can, in some instances, alter gene function and effect neurodevelopment. Several recurrent CNVs are associated with elevated risk for ID, as well as other co-morbid phenotypes such as schizophrenia and epilepsy. For example the 22q11.2 deletion syndrome is associated with ID, but is also is one of the strongest risk factors for psychosis (Schneider et al., 2014).

Individuals with ID face obstacles accessing both physical and mental health services and health inequalities have been described (Emerson, Baines, Allerton, & Welch, 2012). Understanding the genetic aetiology of ID could help to address some of these inequalities by facilitating individualised care plans. For example there are clinical management guidelines available for the 22q11.2 deletion syndrome. Screening for specific physical health conditions,

including cardiac, renal and immunology investigations, and a comprehensive mental health assessment are recommended (Habel et al., 2014). Such guidelines offer good prospects for early intervention and optimised healthcare, although they are not yet available for every genetic cause of ID.

In the UK infants and children presenting with developmental delay are often seen by paediatricians, who can initiate genetic investigations and where appropriate refer onto specialist child and adolescent mental health services (CAMHS). Adult services are generally provided by specialist ID psychiatrists. Referrals for genetic testing can be made to National Health Service (NHS) Regional Genetics Centres (RGCs), which offer clinical genetics expertise in syndromes, cascade testing and counselling. Inequities in access to genetic testing have, however, encouraged the mainstreaming of genetic investigations, with an increased emphasis placed on medical specialists ordering tests directly (PHG foundation, 2011).

ID is often associated with co-morbid psychiatric disorders and/or behavioural problems. Recent estimates from United Kingdom (UK) primary care records show that approximately 21% of individuals with ID have a psychiatric disorder, 25% have some record of challenging behaviour and 49% had been prescribed psychotropic drugs (Sheehan et al., 2015). Given that the investigation of the cause of ID predominately occurs at diagnosis in childhood, there is a large cohort of adults, many with later onset psychiatric disorders, who have not had a diagnostic assessment utilising the latest genetic technologies (Baker, Raymond, & Bass, 2012). We recently recruited 202 adults with idiopathic ID from UK psychiatry services and found that 11% had undiagnosed clinically relevant CNVs (Wolfe et al., 2016).

Whilst the role of specialist clinicians in ordering/referring for genetic testing is evolving, little is known about current views and practices. We aimed to explore the attitudes and practices

of UK psychiatrists working in CAMHS and adult ID psychiatry services on genetic testing in ID.

Method

Psychiatrists from UK CAMHS and adult ID psychiatry services were surveyed as to their attitudes towards and current use of genetic investigations using an online survey.

Survey

The questions were developed through consultation with ID psychiatrists, a clinical geneticist, a genetic counsellor, a genetic researcher and a statistician. Following a pilot, a number of the questions were amended and the opportunity for open text responses was enabled. The 28-item self-administered survey composed of yes/no responses, multiple choice Likert-scale questions, numeric outcomes and free text responses (available in the appendix). The survey was programmed not to force answers to questions and enable completion of the survey with missing responses and administered via the online service tool Survey Monkey (SurveyMonkey Inc. Palo Alto, California, USA).

Participants

The survey was distributed to members of the Faculty of Child and Adolescent Psychiatry and members of the Faculty of Psychiatry of Intellectual Disability via the Royal College of Psychiatrists mailing list. Psychiatrists were invited by email to participate in the survey. A participation reminder was sent after 1 week. Respondents were removed from the analysis if they were junior trainees or listed professions other than CAMHS psychiatry and adult ID psychiatry, if they lived outside the UK and if they had not seen any patients with DD/ID in the previous 12 months.

Statistical analysis

Quantitative statistical analyses were undertaken using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp, Armonk, NY, USA). The analysis compared CAMHS psychiatrists (referred to henceforth as child psychiatrists) and adult ID psychiatrists (referred to henceforth as ID psychiatrists). Continuous outcome variables were analysed using a t-test where the data was normally distributed and Mann-Whitney U test for non-normally distributed data. The chi-squared test was utilised to test categorical outcome variables. Binary logistic regression was undertaken to test univariable factors related to ordering a genetic test. For Likert scale responses the data was collapsed from 5 to 3 scale responses by merging 'strongly agree' with 'agree' and 'strongly disagree' with 'disagree', or 'very frequently' with 'frequently' and 'very rarely' with 'rarely'. To compare clinical confidence ratings, a composite confidence score was generated by assigning the 5 point Likert scale responses a confidence value ranging from 1 for strongly disagree to 5 for strongly agree. These scores were then summed across the eight confidence measures to obtain an overall composite confidence score. Where analyses have been undertaken on a subset of the dataset due to missing values the number of respondents in the analysis has been indicated. Significance has been set at 0.006 to account for multiple testing.

Thematic analysis

Open text responses were thematically coded using Nvivo qualitative data analysis software (QSR International Pty Ltd. Version 10, 2012). Three open text questions were included in the survey, focusing on the benefits and concerns of genetic testing in clinical practice. For the word cloud all open text responses were included and a word frequency analysis was undertaken using Nvivo. Word stemming was undertaken to combine variations of words

from the same root (e.g. genetic and genetics). All words mentioned greater than 5 times, excluding common words, were inputted into Wordle ™ (http://www.wordle.net/) for the creation of the word cloud.

Results

Responses were received from 215 clinicians, comprising 121 child psychiatrists (56%) and 94 ID psychiatrists (44%); 56% were females (n=121) compared with males (n=94, 44%). The majority of respondents worked in England (n=170, 80%), followed by Scotland (n=29, 14%), Wales (n=9, 4%) and Northern Ireland (n=5, 2%).The majority of respondents worked in community teams (n=115, 57%) followed by specialist assessment inpatient units (n=23, 11%) and specialist referral centres (outpatient) (n=19, 9%). A further 46 respondents (23%) reported that they worked in more than one of these settings. The median number of years working in the speciality was 10 (child psychiatrists 10 years, ID psychiatrists 11 years).

Attitudes towards genetic testing

Respondents were asked to estimate the percentage of people with ID for whom genetic factors make a significant contribution towards the cause of their ID. Estimates from child psychiatrists (*Mean*=42%, *SD*=24.7, *Range*=2-100%) were comparable to those of ID psychiatrists (*Mean*=39.6%, *SD*=23.1, *Range*=3-90%) (n=206, *Mean difference* =2.4, 95% CI (-4.25, 8.1) p=0.48). However estimates by both child and ID psychiatrists of the percentage of patients on their caseloads with an established genetic diagnosis were much lower. ID psychiatrists estimated a higher percentage of their own patients to have an established genetic diagnosis (*Median*=10%, *Range*=0-70%) compared to child psychiatrists (*Median*=5%, *Range*=0-100%), (n=205, U=3661.5, *Mean rank* = 120 vs *Mean rank* = 90, p=<0.001).

Ordering of genetic tests

More ID psychiatrists(77%), compared with child psychiatrists (56%), had ordered a genetic test in the last 10 years (n=162, χ^2=8.08, p=0.004). Respondent's estimates of the percentage of ID caused by genetic factors did not influence the likelihood of them ordering a genetic test (n=157, OR 1.01, 95% CI (0.99-1.03), p=0.19). The percentage of patients on respondents' caseloads with an established genetic diagnosis also did not affect the likelihood of ordering a genetic test (n= 156, OR 1.02, 95% CI (0.99-1.05), p=0.33).

Confidence in the genetic testing process

Respondents were asked how confident they felt in eight aspects of the genetic testing process, as presented in Table 1. Child psychiatrists had a lower average total confidence score (*Mean*=22.1, *SD*=6.8) in comparison with ID psychiatrists (*Mean*=27.4, *SD*=5.5). (n=186, *Mean difference*=5.3, 95% CI (3.42, 7.1), p=<0.001). In comparison with child psychiatrists, ID psychiatrists agreed that they were confident in: knowledge of genetic tests (69% vs 29%); assessing for dysmorphic features (63% vs 47%); ordering (47% vs 24%) and interpreting genetic tests (35% vs 12%); genetic counselling (22% vs 12%) and feeding back test results to patients (64% vs 32%) and their families (68% vs 34%).

Concerns with the genetic testing process

Respondents were asked what their main concerns were in relation to the genetic testing process, see table 2. Both child and ID psychiatrists agreed that lack of available treatment was one of the main concerns (58% vs 51% retrospectively). Another main concern was lack of resources, 54% of child and ID psychiatrists agreed that this was a concern. Implications for insurance were a bigger concern for child psychiatrists in comparison to ID psychiatrists (50%

vs 38%), whereas issues around counselling were a bigger concern for ID psychiatrists (53% vs 43%).

Feedback of results and clinical management

As seen in figure 1 both child and ID psychiatrists agreed that a genetic diagnosis is more beneficial for family members than patients. In comparison with child psychiatrists, ID psychiatrists were more inclined to agree that a diagnosis is beneficial for family members (85% vs 78%) (figure 1A) and patients (58% vs 50%) (figure 1B).

Respondents were also asked how they fed back results to their patients with ID. Of the 146 respondents 8 (5%) had utilised videos, 20 (14%) had received input from speech and language therapists, 48 (33%) had used easy read materials, and 98 (67%) had used none of these aids. Responses were comparable for child and ID psychiatrists.

Figure 2 shows respondents' views and experiences of clinical management changes following genetic diagnoses. Respondents agreed that a genetic diagnosis would help with patient clinical management (75% ID vs 62% child) (figure 2A), however few agreed that they had seen frequent management changes in their patients (11% ID vs 12% child) (figure 2B).

Referral to genetics services

Respondents were asked if they had ever ordered a genetic test or made a referral to a clinical genetics service. Those who had made a referral were also asked to estimate the number of referrals in last year. A significantly higher percentage of ID psychiatrists, compared with child psychiatrists had ordered a test or made a referral (90% vs 68%, n=214, χ^2=15.92, p =<0.001). ID psychiatrists also referred more patients per year to the genetics clinic compared with child

psychiatrists (n=153, *Range* = ID 0-25, child 0-10, U= 2161.5, *Mean rank* = 87 vs *Mean rank* = 67, p=0.004).

Respondents were asked what the main reasons for referral to clinical genetics services were. Of the 155 respondents the most frequent reason for referral was presence of dysmorphic features (46% child, 57% ID) followed by intellectual disabilities (31% child, 38% ID). The least likely reason for referral was pharmacological treatment (2% both child and ID).

Service structure and training

Both ID and child psychiatrists agreed that closer links with regional genetics services would be helpful (83% vs 72%, n=197). Respondents were also in agreement that they would prefer to refer to a regional genetics service rather than order a genetic test themselves (child 85%, 77% ID n=195). Finally there was a consensus that further training in genetics would be beneficial (child 71%, 66% ID, n=195).

Thematic analysis

Four main themes were identified from the 76 respondents who completed the open response questions comprising: family concerns, clinical management, and access to services and training.

Of the 23 respondents who reported family concerns the most frequent benefits identified were relief from guilt and increased understanding of the patient's condition, followed by ability to access a support group and family planning. Respondents who discussed clinical management tended to mention the positive aspects, such as tailored medical and psychiatric interventions and clarification of syndrome specific behaviours. Only three respondents

stated that they did not think a genetic diagnosis was helpful for clinical management. One respondent commented "*it is something of a paradox that the advances in the understanding of genetics and its potential impact upon our patient group has not translated into a significant increase in the use of genetic testing to help with diagnosis and care planning. I can only surmise that the social model of Disability as outlined in Valuing People has steered the diagnostic process away from genetic labelling*".

Access to genetics services was mentioned by 22 respondents, who described problems with referring to genetics services and the variable levels of knowledge of professionals involved in the pathway. There was concern that psychiatrists, who have not specialised in genetics, do not have the skills to refer directly for genetic testing. Good working relationships with genetics services were said to be a valuable resource. Five child psychiatrists stated that they would defer to their paediatric colleagues to make decisions about genetic testing.

Several respondents felt that current training in genetics was insufficient and is not keeping abreast of technological advances. It was suggested that quick reference guides and screening tools would be valuable resources to support the decision making process. See figure 3 for a word cloud of the most frequently used words in the open text responses (results from both professional groups as responses were comparable for child and ID psychiatrists) and a summary of positive and negative opinions for each of the main themes.

Discussion

Our results indicate that the majority of child and ID psychiatrists working with patients with ID are already ordering genetic tests or making referrals to genetics services. However, there are several disparities in clinical genetic practices. In comparison with child psychiatrists,

adultID psychiatrists reported: a higher number of patients with genetic diagnoses, greater confidence in the genetic testing process, higher numbers of tests ordered and more patients referred per year to genetics services.

Respondents were asked to estimate the percentage of ID caused by genetic factors. The responses varied greatly with some respondents estimating as low as 2% and others as high as 100%. Although both child and ID psychiatrists had similar mean estimates (39.6% and 42%) of the percentage ID caused by genetic factors, these estimates were much higher than the actual percentage of patients on caseloads with a known genetic diagnosis (median=10% ID and median=5% child). It is unclear why this disparity exists. It would be interesting to investigate whether the clinician responsible for ordering genetic testing is communicating the results to other professionals involved in the individual's care. This will be particularly important for individuals with ID and co-morbid diagnoses who are under the care of multiple medical professionals.

A high proportion of ID psychiatrists (77%) and just over half of child psychiatrists had directly ordered a genetic test. In comparison with child psychiatrists, ID psychiatrists were significantly more likely to order a genetic test and also referred more patients to the genetics clinic per year. This may have in part been a reflection of the ID psychiatrist's greater reported confidence in the genetic testing process. As evidenced in table 1, ID psychiatrists were significantly more confident in all aspects of the testing process, apart from capacity testing which is likely to be more complex in adulthood. One explanation for ID psychiatrists being more confident and ordering/referring for more genetic tests is due to the different structures of child and adult ID psychiatry services. Some child psychiatrists reported that they would defer to paediatric colleagues for opinions on genetic testing.

The survey highlighted a number of barriers to genetic testing in clinical ID services. Both child and ID psychiatrists reported that they were concerned about lack of available treatment and resources for genetic testing. Interestingly child psychiatrists had specific concerns about implications for insurance. The Department of Health have released a moratorium extending until 2019 whereby the only genetic test required to be disclosed is for Huntington's disease on life insurance sums worth more than £500,000 (HMGovernment, 2014). Therefore results from CMA should have no impact on insurance premiums and this misconception could be a barrier to clinicians ordering/referring for genetic testing. ID psychiatrists expressed concern about issues surrounding counselling. Feedback of genetic diagnoses to adults with ID is understandably more complex than feedback to parents of children with ID and this could be an important area for additional resources and research.

Both child (85%) and ID (77%) psychiatrists agreed that they would prefer to refer to an RGC rather than directly order a genetic test themselves, however links with NHS RGCs appeared to be variable. Some respondents reported good links with their local genetics services, whilst others felt that access to service was a barrier to referring for genetic testing. Both ID (83%) and child psychiatrists (72%) felt that better links with genetics services would be beneficial. Many of these clinicians felt that they do not have the knowledge or training to order genetic tests directly. This finding is supported by another survey, which found ID psychiatrists lacked adequate knowledge about genetics and testing processes ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1192/pb.bp.111.038216", "ISSN" : "1758-3209", "author" : [{ "dropping-particle" : "", "family" : "Villiers", "given" : "J.", "non-dropping-particle" : "de", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Porteous", "given" : "M.", "non-dropping-particle" : "", "parse-names" : false,

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The majority of respondents expressed a wish for further training (71% child, 66% ID). Neither child and adolescent nor ID psychiatry curricula currently have learning objectives that specifically cover genetic disorders associated with ID (http://www.rcpsych.ac.uk/traininpsychiatry/corespecialtytraining/curricula.aspx). The curricula also fail to cover the genetic work-up and basic genetic counselling skills that are required to take more of an active role in identifying and managing patients with genetic disorders. However, there are several recent initiatives to improve the psychiatry curriculum. For example, the Gatsby-Wellcome initiative aims to ensure that training focuses more on scientific advances in basic and clinical neurosciences (http://www.rcpsych.ac.uk/traininpsychiatry/corespecialtytraining/neuroscienceproject.aspx). It is, therefore, hoped that future cohorts of psychiatrists will be more confident in utilising technological advancements in the assessment and management of their patients.

One of the reasons for undertaking genetic investigations is that a genetic diagnosis is likely to provide information about specific associated medical and psychiatric phenotypes and thus

could improve treatment plans and clinical management for the patient. Whilst the majority of respondents felt that a genetic diagnosis would help with clinical management, fewer patients on their caseloads had a genetic diagnosis than they would expect and clinical management changes following genetic diagnoses were not frequently seen in practice. There are published medical guidelines available for several genetic disorders, for example via the Orphanet portal for rare diseases (http://www.orpha.net/), and information guides on an extensive range of chromosomal disorders are available from the support group Unique (http://www.rarechromo.co.uk/html/DisorderGuides.asp). It would be of interest for further research to investigate whether psychiatrists are aware of these guidelines when they receive a genetic diagnosis for their patient.

Another important consideration is that knowledge of behavioural phenotypes can place psychiatrists in a better position to deliver appropriate interventions and environmental adaptations. Whilst there is within syndrome variation it has been shown that certain behavioural features, such as repetitive and self-injurious behaviours, are more common in particular syndromes. There are also implications for health screening, for example gastro-intestinal problems are common in Cornelia de Lange syndrome and can exasperate self-injurious behaviours (Waite et al., 2014). A recent survey of ID professionals found that nine out of ten professionals interviewed felt that specific knowledge of a neurodevelopmental syndrome should play a key role in healthcare provision. A specific genetic diagnosis was particularly thought to prompt proactive screening for related physical and mental health problems, which is of particular benefit for patients with severe impairments (Redley, Pannebakker, & Holland, 2016). One of the main challenges in practice is that individual

syndromes are rare and psychiatrists are unlikely to care for many individuals with the same disorder, although the overall burden of rare syndromic disorders is large.

Both child and ID psychiatrists agreed that receiving a genetic diagnosis was more beneficial for family members than for the patient. Research has shown that there is a benefit to mothers in receiving a diagnosis for a child with ID; however there is a lack of research as to the impact of a genetic diagnosis for adults with ID (Lingen et al., 2016) Several respondents reported that a diagnosis can help to alleviate guilt for family members, as well as increasing understanding of the patient's syndrome specific behaviours and enabling valuable access to support groups. It seems that respondents were able to report on a range of psychosocial benefits, which could indirectly improve patient management, however tangible changes in clinical decision making following a genetic diagnosis were less easy to define.

Limitations

The survey was self-reported which could have led to biases in estimations. There may have been a selection bias in the clinicians who chose to respond to the survey, perhaps those with more extreme views on genetics were more inclined to respond. This survey specifically focused on psychiatrists, who are one of the medical specialists frequently in contact with patients with ID in the UK. These findings may not be generalisable to other countries where services are organised differently

Conclusions

Whilst a high number of child and ID psychiatrists appear to already be ordering genetic tests there remains a preference for referring directly to clinical genetics services. Respondents

highlighted several areas of the genetic testing process in which they particularly lack confidence, such as indications for testing, interpretation and feedback of genetic results. Child psychiatrists in particular felt less confident, ordered fewer genetic tests and referred fewer patients to genetic services.

Genetic investigations are continuing to advance at a very rapid pace, with exome and whole genome sequencing beginning to enter clinical practice. In conjunction with other genetic investigations it is likely that a genetic diagnosis will be identifiable in a much higher proportion of patients with ID in the future. This should facilitate early diagnosis and tailored interventions for patients and their families. However as the landscape of genetic investigations becomes more complex it is going to be a challenge for psychiatrists to keep pace of developments. Improvements in training and closer links with genetics services would appear to be key areas to address to meet this challenge.

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