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Autism and heritable bone fragility: A true association?

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ABSTRACT

Objectives: Osteogenesis Imperfecta (OI) is a heterogeneous condition mainly characterised by bone fragility; intelligence is reported to be normal. However, a minority of children seen also show symptomology consistent with an 'Autism Spectrum Disorder'. A joint genetics and psychology research study was undertaken to identify these patients using 'Gold Standard' research tools: Autism Diagnostic Inventory Revised (ADI-R); Autism Diagnostic Observation Schedule (ADOS) and undertake genetic analyses in them.

Method: A cohort of $n = 7$ children with autistic traits and severe/complex OI were recruited to the study. The study was set-up to explore whether there was a genetic link between bone fragility and autism in a sub-set of patients with bone fragility identified with autism traits in our complex/severe OI clinic. This was not set-up as a prevalence study but rather an exploration of genetics in association with ADI/ADOS confirmed ASD and bone fragility.

ADI& ADOS: Standardised tools were used to confirm autism diagnosis. ADI and ADOS were completed by the Clinical Psychologist; ADI comprises a 93 item semi-structured clinical review with a diagnostic algorithm diagnosing Autism; ADOS is a semi-structured assessment of socialisation, communication and play/imagination which also provides a diagnostic algorithm.

Exome sequencing: In patients recruited, those that fulfilled research criteria for diagnosis of autism using above tools were recruited to trio whole exome sequencing (WES).

Results: one patient had compound heterozygous variants in *NBAS*; one patient had a variant in *NRX1*; one patient had a maternally inherited *PLS3* variant; all the other patients in this cohort had pathogenic variants in *COL1A1/COL1A2*.

Conclusions: Although, not set out as an objective, we were able to establish that identifying autism had important clinical and social benefits for patients and their families in ensuring access to services, appropriate schooling, increased understanding of behaviour and support.

Lay summary: It is important for clinicians looking after children with brittle bone disease, also referred to as Osteogenesis Imperfecta (OI) to be aware of early features of developmental delay/autistic traits especially with severe forms of OI as the emphasis is on their mobility and bone health. Ensuring appropriate assessment and access to services early-on will enable these patients to achieve their potential. Further investigations of genomics in bone fragility in relation to autism are required and dual diagnosis is essential for high quality clinical and educational provision.

1. Introduction

Osteogenesis imperfecta is a heterogeneous group of disorders characterised by bone fragility and fractures. Extra-skeletal features such as hearing loss, dentinogenesis imperfecta and joint hypermobility can also be variably present. The condition can be inherited in an autosomal dominant or recessive pattern, or can be caused by a sporadic mutation (*de novo*) in a proband (Balasubramanian M. Clinical and

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Molecular Heterogeneity of Osteogenesis Imperfecta, 2017). Osteogenesis imperfecta is the most common form of inherited bone fragility disorder, with an estimated prevalence of 1 in 15,000 live births (Folkestad et al., 2017). Incidence is approximately 1/15,000–1/20,000 live births but this may be underestimated, as milder forms may not have come to medical attention (Forlino and Marini, 2016).

The classification of this disorder was traditionally based on severity and inheritance. Previously, the four main types of osteogenesis imperfecta have been separated into the following distinct categories (Sillence et al., 1979). A greater understanding of genetics has led to an extension of the classification of OI. Over 85% of mutations causing OI are in the type 1 collagen genes (*COL1A1* or *COL1A2*); the most common being the replacement of a glycine amino acid in the $(Gly – X – Y)_n$ repeating unit within the collagen triple helix. Apart from the type 1 collagen gene, many other genes are now confirmed to be associated with OI. Recurrent mutations in *IFITM5* have been implicated in the aetiology of Type V OI, which has an AD pattern of inheritance (Semler et al., 2012; Cho et al., 2012).

OI Types VI-IX are inherited in an autosomal recessive (AR) pattern (Gensure et al., 2005; Glorieux et al., 2002; Glorieux, 2005). Other genes such as, *CRTAP*, *P3H1, FKBP10*, *PPIB*, *SP7*/Osterix (*OSX*), *SERPINF1*, *SERPINH1*, are associated with AR forms of OI (Alanay et al., 2010; Baldridge et al., 2008; Christiansen et al., 2010; Lapunzina et al., 2010; van Dijk et al., 2009). These forms are typically very severe if not lethal. More recently several other recessive forms of OI- *TMEM38B/BMP1/CREB3L1/SPARC* have been characterised (Shaheen et al., 2012; Martínez-Glez et al., 2012; Symoens et al., 2013; Mendoza-Londono et al., 2015) and X-linked forms of OI (*PLS3/MBTPS2*) (van Dijk et al., 2009; Lindert et al., 2016) and heterozygous variants in *WNT1/LRP5* (Laine et al., 2012; Hartikka et al., 2005) making OI a very genetically heterogeneous condition and perhaps use of heritable bone fragility as a more appropriate terminology to describe this group of conditions.

Rarely patients may present who do not fit into the sub-categories of this extended OI classification. This may be because they have not yet suffered a fracture, or because they present with other pathologies, such as the syndromal features of facial dysmorphism, craniosynostosis or contractures. They may have extreme short stature or developmental delay. In these cases, it may be that the patient has an atypical diagnosis of a type I collagenopathy (Balasubramanian et al., 2016). Some patients with bone fragility display autistic traits which are not in keeping with their clinical diagnosis as children with OI are reported to have normal intelligence; this would be classified as 'atypical bone fragility'.

In the UK, the prevalence of autism is 1 in 100 (Baird et al., 2006). Over the last 5 years, in our centre which has a large cohort of bone fragility patients, it was our clinical observation that an unexpectedly high number of children with bone fragility are also presenting with clinical traits of ASD as characterised in DSM V (2013) (Autism Spectrum Disorder 299.00 (F84.0) DSM-V, American Psychiatric Association, 2013) (n = 10–15/102). We observed that the rate of affected children appeared to be higher than expected from the latest ASD population prevalence estimates of 1.9% (Baird et al., 2006) and decided to study this in further detail. There is sparse evidence for this association in the literature but in our clinical practice we have noted a clear association, which seems more pronounced in children with relatively severe bone fragility.

The DSM V diagnostic criteria for ASD specify a child or adult must show a) persistent deficits in social communication and social interaction, b) restricted and repetitive patterns of behaviour, c) symptoms must be present in early developmental period, d) symptoms must cause impairment in functioning and e) symptoms must not be better explained by developmental delay. This study explored the association between bone fragility and autism spectrum disorder in further detail and set out to describe a novel phenotypic association.

2. Materials and methods

The research involved participation of children with OI from the nationally-commissioned Severe and Complex OI group (total 102 children). Participants were recruited into a research project to study the association of autism and OI and establish genotype: phenotype correlations. Funding was obtained from the Newlife Charity and ethical approval was obtained from the local regional ethics committee (REC reference: 15/YH/0196) to undertake phenotyping and genetic work-up in this group of patients.

From this group, we selected patients aged between 3 and 16 years (total of 10 patients), who were reported to have difficulties with social interaction by the multi-professional team. The Senior Clinical Psychologist assessed these patients clinically for those who show signs of ASD (n = 10 children were noted to have atypical social skills, 7 of these families were approached; all of them consented to participate in the study). 3/10 patients: it was decided by the clinical team to not approach children in whom atypical social skills were noted as it was felt by the multidisciplinary team that the families would not be able to deal with a diagnosis of autism in addition to the severe bone fragility. Following informed consent from parents and their carers and where applicable, assent from children, eligible children were recruited to the study. This was not set out as a prevalence of autism in bone fragility study (planned as a next step) but it is likely from our observation that may be as high as 10% in our cohort.

Recruited children were screened for ASD traits using standardised ASD clinical research tools. Sub-group of children who screened positive for ASD underwent a dysmorphology assessment and genetic testing to identify common genotypes within this sub-group. We discussed results with families and onward referral to local child development centres in those that fulfilled diagnostic criteria. This optimised follow-up and support for families within ASD services locally along with continued support within OI services.

2.1. ASD screening

Recruited children were screened by the Senior Clinical Psychologist using the Autism Diagnostic Inventory – Revised (ADI-R) and Autism Diagnostic Observation Schedule (ADOS).

2.1.1. Standardised psychological tests

2.1.1.1. ADI-R (Autism Diagnostic Inventory Revised) (Le Couteur et al., 2008). The ADI-R is a clinical diagnostic instrument for assessing autism in children and adults. It provides a diagnostic algorithm consistent with DSM-IV and ICD-10 criteria for ASD. It consists of a 93-item semi-structured interview for parents/carers of people with suspected ASD. The ADI-R scores are categorised into three domains of communication and language, social interaction and restricted/repetitive behaviours. A classification of ASD is given when scores in all three domains meet specified cut-offs. The assessment can be conducted from 4 years of age to adult.

2.1.1.2. ADOS (Autism Diagnostic Observation Schedule) (Lord et al., 1997). The ADOS is a semi-structured assessment and observation of socialisation, communication and restricted/repetitive behaviours. The ADOS is completed by the clinician directly with the child and includes various activities designed to elicit behaviours that are coded to inform an ASD diagnosis. Sub-sections are coded using an algorithm; children score in the categories of Non-spectrum, Autism or Autism-Spectrum. The assessment can be conducted from 12-months of age to adult.

From this group, children identified as having ASD using ADI-R and ADOS were included for genetic assessment.

2.2. Genetic assessment

From the children recruited, those that screened positive for a