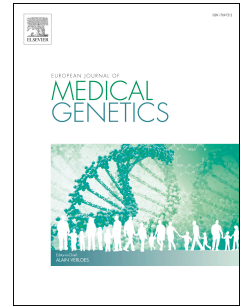


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Two patients with chromosome 22q11.2 deletion presenting with childhood obesity and hyperphagia

J.K. Bassett, K.E. Chandler, S. Douzgou



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JK Bassett¹, KE Chandler^{2,3}, S Douzgou^{2,3*}

1. Faculty of Health and Medicine, Lancaster University, Lancaster LA1 4YG, UK.

2. Manchester Centre for Genomic Medicine, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Sciences Centre, St Mary's Hospital, Manchester M13 9WL, UK. Email: sofia.douzgou@cmft.nhs.uk. Telephone: 01612766268*

3. Institute of Human Development, University of Manchester, Oxford Road, Manchester, M13 9WL, UK.

***Corresponding author**

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Keywords: 22q11.2 deletion, obesity, hyperphagia, Prader-Willi Syndrome

Abstract

Chromosome 22q11.2 deletion syndrome is a clinically heterogeneous condition of intellectual disability, parathyroid and thyroid hypoplasia, palatal abnormalities, cardiac malformations and psychiatric symptoms. Hyperphagia and childhood obesity is widely reported in Prader-Willi Syndrome (PWS) but there is only one previous report of this presentation in chromosome 22q11.2 deletion syndrome. We describe two further cases of chromosome 22q11.2 deletion syndrome in which hyperphagia and childhood obesity were the presenting features. This may be a manifestation of obsessive behaviour secondary to some of the psychiatric features commonly seen in chromosome 22q11.2 deletion syndrome. Serious complications may result from hyperphagia and childhood obesity therefore early recognition and intervention is crucial. Due to the similar clinical presentation of these two patients to patients with PWS, it is suggested that the hyperphagia seen here should be managed in a similar way to how it is managed in PWS.

Introduction

Chromosome 22q11.2 deletion syndrome (22q11.2delS) is characterised by intellectual disability, parathyroid and thymic hypoplasia, palatal abnormalities, facial dysmorphisms, short stature and cardiac outflow tract malformations [1] [2]. A significant and common component of 22q11 deletion syndrome are its neuropsychiatric features, most notably autistic spectrum disorder (ASD), obsessive compulsive disorder (OCD), and schizophrenia in later life [3].

Hyperphagia and obesity is a major feature of Prader Willi syndrome (PWS), manifesting as poor feeding in the first year of life due to a poor suckling reflex and hypotonia, followed by hyperphagia and obsessive and abnormal behaviour around food such as hoarding, gorging and eating non-food items from around age 2 [4]. The hyperphagia seen in PWS is a significant problem as it can lead to morbid obesity in adolescence and adulthood as well as stomach rupture, cardiovascular disease, sleep apnoea and thrombophlebitis if not treated early.

Although there are some known cases of 22q11.2delS in patients with obesity [5], only a single patient with 22q11.2 has been reported with childhood hyperphagia [6]. We report on two additional cases of children with confirmed 22q11.2delS who presented in our clinics with these features.

Case 1

An 11 year old boy presented with small and undeveloped genitalia, delayed puberty, learning difficulties, severe speech delay and obesity.

He was the 4th child to healthy non-consanguineous parents. His siblings were healthy. There was no history of familial obesity. He was born at 37 weeks by spontaneous vaginal delivery with a birth weight of 3.17kg. As a neonate he was lethargic and had poor feeding including vomiting. Initially his weight gain was poor, however by age 3 years, he started to eat excessively and became obese, displaying food seeking and aggressive behaviour if access to food was difficult. By 12 years he weighed beyond

the 99.6th centile (69.5kg) and his height was on the 50th centile (145cm), for a BMI of 33.

He had recurrent chest infections in early childhood. He manifested global developmental delay and attended mainstream school with support for moderate learning difficulties.

He presented with behavioural problems including urinating and showing his genitals in public. He also displayed a lack of imaginative play and was uninterested in engaging with other children. At the age of 8 years he was diagnosed with severe OCD and anxiety in the context of ASD and was started on treatment with a selective serotonin reuptake inhibitor (SSRI).

By 11 years and 4 months he showed no signs of puberty. His penis was impeded in pubic fat and measured 4cm. Both testes were present and had an equal volume of 3cm. He lacked both pubic and axillary hair.

The patient had dysmorphic features including almond-shaped eyes, hypertelorism, flat philtrum, epicanthic folds, short palpebral fissures, notched nasal tip and a flat nasal bridge. He had nasal speech that was difficult to understand.

An echocardiogram and audiometry showed normal results. A renal ultrasound showed right renal agenesis. Urea and electrolytes were normal. He had a slightly raised creatinine as well as IgA levels and low IgM levels.

Case 2

A five year old girl presented due to concerns regarding eating behaviour including excessive over-eating and weight gain.

She was the 4th child of healthy of non-consanguineous parents. All previous children were healthy; a maternal aunt had pulmonary stenosis. There was no history of familial obesity. During pregnancy she was found to have echogenic bowel and a single umbilical artery. Umbilical cord compression at delivery resulted in an emergency caesarean section at 38 weeks. Her birth weight was 3.25kg.

She initially had no feeding problems, however following weaning to solids she developed a large appetite. At 13 months, following surgery for the correction of patent ductus arteriosus, she started gaining weight. By age 6 her weight was on the 99th centile (37.4kg), height was on the 91st (121.3cm) and head circumference between the 2nd and 9th (50cm). Her parents experienced difficulties in controlling her constant, food-seeking behaviour. She developed significant truncal obesity with gynaecomastia.

She suffered from recurrent chest infections in early childhood as well as an episode of orbital cellulitis.

She manifested developmental delay: smiled by 9 weeks, sat unsupported by 9 months, crawled by 13 months and walking by 19. There were no concerns about her speech or social interaction, although she did prefer to play with adults over her peers.

She displayed imaginative play and there was no evidence of obsessions or rigid behaviours. She was both faecally and urinary incontinent and remained in nappies during the day. She attended mainstream school with one-to-one full time support for special educational needs. She was also found to have a short attention span and was easily distracted.

She had over-folding of her upper helix but otherwise resembled both her parents. She had hyper-extensible finger, knee and ankle joints bilaterally with femoral anteversion. She was noted to have long curved fingers and flat, laterally deviated feet which were painful with deambulation.

She had a normal audiology test. Her full blood count, immunoglobulins, lymphocytes, serum calcium, and thyroid function tests were all normal.

Genetic Testing

On the basis of their clinical presentation both patients had DNA methylation testing for chromosome 15q11-q13 which showed normal results.

In patient 1 microarray analysis of peripheral blood using an OGT ISCA 8x60K oligo array interpreted with CytoSure Interpret v4.5 software with the genome build, GRCh37 at a resolution of 180kb found a recurrent 22q11 microdeletion (46,XY.arr[hg19] 22q11.21 (18,818,376 – 21,540,347) x 1), totalling approximately 2.7Mb on microarray analysis. In patient two the same method was used, indentifying a recurrent 22q11 microdeletion (46,XY.arr[hg19] 22q11.21 (18,894,820 – 21,025,719) x1) totalling approximately 2.1 Mb on microarray analysis.

Following the positive microarray result, both parents had in situ hybridisation studies with a Kreatech TBX1 probe to 22q11.2 from a blood cell culture sample. The microdeletions were found de novo in both patients.

Discussion

While obesity in 22q11.2delS has been reported [5], some studies have shown that the average BMI of 22q11.1 patients is no different to the general population [7]. However in the two cases presented here, sudden weight gain and excessive eating with aggressive behaviour if food was withheld were prominent features of the presentation, to the extent that two independent clinical geneticists requested testing for PWS.

Interestingly, the pattern of feeding problems was also similar to those seen in PWS in both patients, with both having poor feeding in the first year of life, followed by the onset of hyperphagia and obesity occurring in early childhood.

Hyperphagia may be a manifestation of obsessive behaviour secondary to ASD sometimes observed in 22q11.2delS [8] [9] and is known to manifest in this way [10].

This has implications for the management of individuals with 22q11.2delS. Treating hyperphagia early is crucial to avoid life threatening obesity leading to cardiovascular

disease, respiratory disease and type II diabetes. Dietary management overseen by a dietician from age 2-10 is an effective intervention [11].

Treatment of behavioural and psychological aspects is also important in mitigating some of the compulsive behaviour related to ASD seen in 22q11.2delS and PWS. General measures to address this include utilising structure and routine to minimise anxiety related to ASD [12]. One therapy that has been shown to be effective against covert food stealing is applied behavioural analysis (ABA) [11]. Pharmacological and surgical treatment of hyperphagia in PWS is of limited effectiveness, however in cases of severe life threatening obesity bariatric surgery may be necessary [11].

As shown in PWS patients with hyperphagia early recognition and intervention can be effective in preventing the complications of severe obesity. Although these interventions have not been assessed specifically in 22q11.2delS, it is likely due to the similar presentation that these may prove beneficial. It is also important for clinicians to be aware of the possibility of hyperphagia in 22q11.2delS so diagnoses are not missed and other aspects of patients treatment is prompt and effective.

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