Case study

De Grouchy syndrome: An unusual presentation of severe short stature in type 1 diabetic children

Abstract

Diabetes mellitus type 1 (DM1) is associated with different clinical syndromes. Some are commonly encountered, like Turner's syndrome, while others are rarely found in clinical practice,namely, de Grouchy syndrome.This is a rare genetic disorder characterised by micro deletions in the short arm of the chromosome 18.

There are many contributing factors for a retarded growth in a diabetic child, for example, poor glycaemic control, associated thyroid disease, celiac disease, and an unusual one is de Grouchy syndrome. In the present article, we report an isolated case of 18p deletion in a 6-year-old female who for the first time reported to the hospital for diabetes mellitus type-1. The patient was short statured with mental retardation and craniofacial, skeletal, dental, and endocrinal abnormalities. The aim of this case report is to increase the awareness about one of the genetic syndromes associated with diabetes mellitus. Asthe clinical features of de-grouchy syndrome is quite variable, it's presentation warrants prompt diagnosis for effective management, especially when associated with life threatened conditions, such as type 1 diabetes mellitus, special in need and severe growth retardation. Furthermore, genetic

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counseling for such patients and their families should be considered as a part of treatment itself.

Keywords: *18p deletion*, *dysmorphic features*, *growth deficiency*, *type diabetes mellitus*mental *retardation*

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Introduction

De- grouchy syndrome refers to a chromosomal disorder resulting from the deletion or absence of all or part of the short arm of chromosome 18 (deletion of distal 18p-) and considered type 1 de grouchy, while deletion of long arm of chromosome 18 is known as de-grouchy type 2. It was first reported in 1963 by the French geneticist Jean de Grouchy, and today the preferred nomenclature for this condition is 18p deletion.

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It is a rare disease; the incidence is estimated to be about 1: 50,000 live-born infants. The female-to-male ratio is 3:2. [1, 2, 3]

Most cases of deletion 18p are supposed to originate from *de novo* deletions, which accounts for 85% of cases.Familial transmission of 18p- from one of the parent to the child has been reported, mostly from maternal side. [4, 5]

Presentation of this syndrome is quite variable with dysmorphic features. The most frequent clinical features consist of mild to moderate growth deficiency, ptosis, epicanthic folds, low nasal bridge, hypertelorism and large protruding ears. Dental problems that include ; irregularly set teeth are of poor quality with generalized enamel hypoplasia and high caries index, lateral incisors are sometimes missing,, multiple root stumps, high palatal arch, geographic tongue, and generalized gingival enlargement [6]. Holoprosencephaly,mental retardation, microcephaly,hypotonia, hearing impairment, Poor coordination, nystagmus and seizures.Foot deformities and clinodactyly of the fifth finger is observed in about 10% and 20% of the cases respectively. [7, 8]. Mental retardation is mild to severe with an average intellectual quotient (IQ) between 45 and 50. There is a significant discrepancy between verbal and non-verbal performance, verbal performance being more severely affected.[9,10]Autoimmune diabetes mellitus diabetes and other

autoimmune disorders have been reported in association with type 2 de grouchy syndrome (deletion 18q) .

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Both Hypothyroidism and hyperthyroidism have been reported in patients with distal 18q. [9]Recent evidences have suggested an association with growth hormone deficiency that responded well to growth hormone replacement therapy. [8]There are also many abnormalities related to sexual development which include underdeveloped labia minora, undescended testes, small scrotum and penis are some of these. [9-10]

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The common method usedfor diagnosis de Grouchy syndrome is Fluorescent in Situ Hybridization (FISH). Prenatal diagnosis can also be made through amniocentesis.[9-11]Genetic counseling is required , Recurrence risk for siblings is low for *de novo* deletions and translocations, but is significant if a parental rearrangement is present.[11]

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The prognosis of this syndrome depends on a number of different factors. These include: the type of de Grouchy syndrome, the severity of the symptoms, and how they develop. An early diagnosis and interventions can improve the outcome and reduces morbidity. [9]

The treatment interventions vary anddepending on the type and severity of the symptoms. Multi-team approach guarantees proper management of this disorders that may associated with this syndrome. Surgery can be used to correct defects or abnormalities that occur. Abnormalities that can be corrected include a cleft palate, heart defects and many sexual development problems. Physical therapy can help improve lack of muscle tone and other physical issues. Speech therapy, educational support, social and vocational services are also recommended. [9, 10]

Case report:

A female patient aged6 yearwas brought to medical attention at the age of 16 months because of severediabetic ketoacidosis.

She was the product of a full term normal vaginal delivery, with a birth weight of 2.250 kg, the neonatal period passed smoothly without complications. She was fed both breast and bottle milk from the beginning.

She is the only girl of her no consanguineous parents, and was preceded by 3 older brothers all of them are healthy, and they had one abortion previously. Her family history is unremarkable for such problems, but is positive for short stature. Other than her diabetes there is no significant events in her history.

During her follow up in our endocrine clinic for her diabetes, shestarted intensified regimen insulin therapy, we noticed that her HbA1c ranged between 8-9,due to poor injection technique.

Her clinical examination was significant for retarded growth. Her mean growth velocity was 2.5 cm/year, and weight was consistently below third centile.

Her investigations revealed hypochromic microcytic anaemia, positive insulin autoantibodies(Anti- Glutamic acid Decarboxylase , highly elevated 179,7 U/ml) , IGF-1 (Somatomedin C) was normal for age and sex 53ng/ml as well as growth hormone level , her thyroid function was normal , and there was no evidence of celiac disease .

When concentrating on her short stature we found out that her mother is 156 cm and her father is 165 cm long, and MPH is approximately 154.5 cm , and her expected adult height will be in the range of 164.5-162.5 cm .Bone age is delayed it is of 24 month old child (4 years delayed) . For further analysis of the true reason behind her short stature, we asked for karyotyping which showed: total number of chromosomes 46, XX,del(18)(p11.2) , which is consistent with de Grouchy syndrome .

Her Cognitive performance is in agreement with mild mental retardation (IQ 85) according to the Wechsler intelligence scale for children, third edition (WISC-III). There is no difference between

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verbal and non-verbal functions. Shewas consideredas special in need and started follow up with a community pediatric specialist.
She was referred to an ophthalmologist to asses her visionAs , notice there was deeply seated- eyes and partial ptosis with no otherremarkable abnormality (photo-1). Dental checks showing irregularly set teeth and missing lateral incisors (photo-2)
MRI of the brain revealed no intrinsic brain abnormalities with normal pituitary gland.
She was started on growth hormone therapy, without any significant improvement in her growth pattern over time.
She was advised to have her hearing checked, and to have abdominal and pelvic ultrasound, Echocardiography,and also to have orthopaedic.

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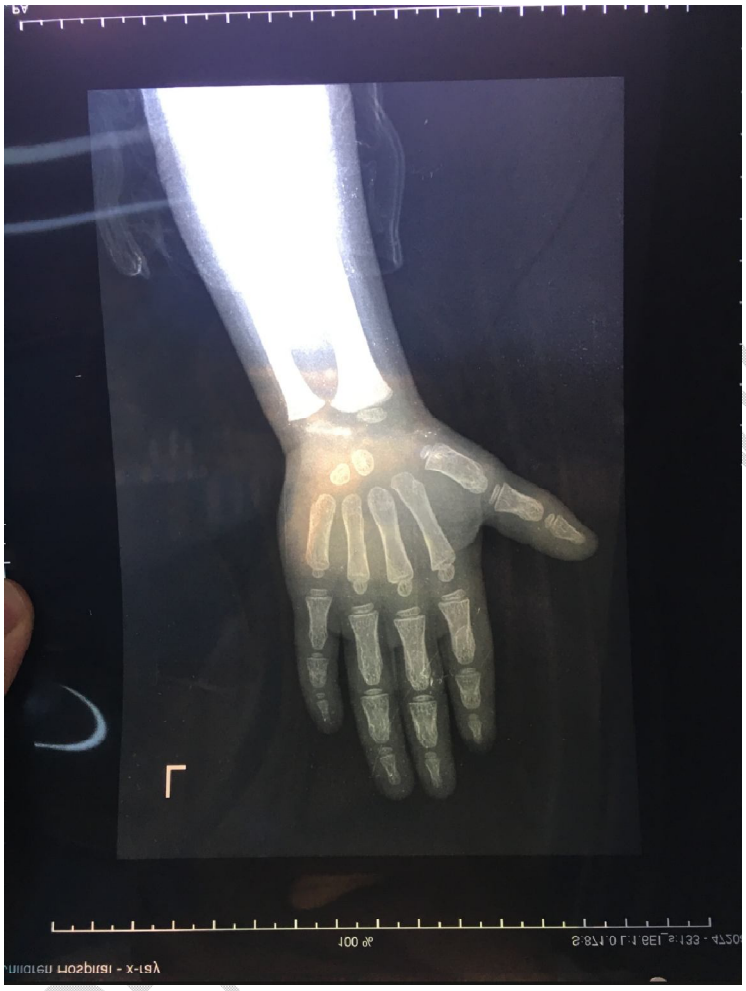
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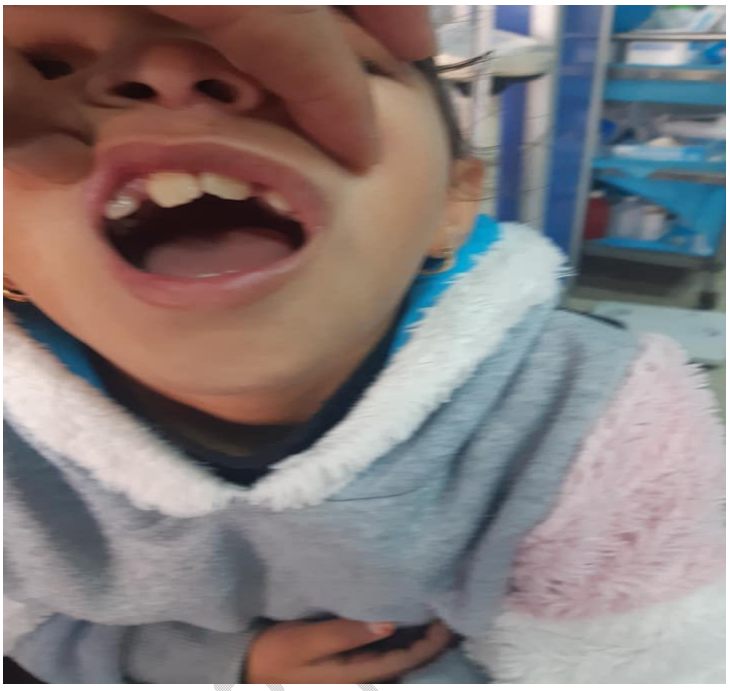
Photograph(1) of the patient showing 1. Deep seat eyes and partial Ptosis 2.low nasal nasal bridge and flattened malar prominence 3.Short protruding upper lip .4. Carp-shaped mouth.



Photograph (2) of the patient; Showingirregularly set teeth andmissing lateral incisors

Discussion

Distal 18p or q- is a deletion of the arm of chromosome 18. The majority of deletions have breakpoints between 45,405,887 and the tip of the chromosome. There are no common breakpoints, thus the size of the deletions vary widely.The largest deletion reported is 30.076 Mb, while the smallest deletion reported to cause a clinical phenotype is 3.78 Mb . This syndrome has different phenotypes with a similar genetic defects,thisis proofedby a study on eight persons whose karyotypes demonstrated deletion of a portion of the long arm of chromosome 18. Seven of these persons who showed the typical del (18q) syndrome had a common deletion in band 18q21, most likely band q21.3, and in at least two persons the deletion was interstitial. Another mentally retarded child, dissimilar in appearance, had a more proximal deletion within band 18q12.

Two different clinical syndromes resulted from deletions of these different segments of the long arm of chromosome 18.[12] another study used new molecular techniques such as array CGH allow for a more precise determination of breakpoints in cytogenetic syndromes, thus leading to better-defined genotype–phenotype correlations. In order to update the phenotypic map for chromosome 18q deletions .Using this approach, we were able to refine the critical regions for microcephaly (18q21.33), short stature (18q12.1-q12.3, 18q21.1-q21.33, and 18q22.3-q23), white matter disorders and delayed myelination (18q22.3-q23), growth hormone insufficiency (18q22.3-q23), and CAA (18q22.3). Additionally, the overall level of MR appeared to be mild in patients with deletions distal to 18q21.33 and severe in patients with deletions proximal to 18q21.31. The critical region for the 'typical' 18q-phenotype is a region of 4.3 Mb located within 18q22.3-q23. [11, 12], Our case has 46,XX,del(18)(p11.2) .

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Our patient does not suffer from any oral malformations , compared to a study that was held in Europe , 33 Dutch and Belgian patients with a deletion of 18q were studied , twenty out of 33 patients (61%) with a deletion 18q had congenital aural atresia (CAA) ranging from narrow external auditory canals to meatal atresia type IIB. Fifteen patients (45%) had conductive hearing impairment (range: 30dB–70dB). Twelve of these 15 patients (80%) received hearing aids, which resulted in improved hearing but not in speech development. CAA was found only in patients with a distal deletion of 18q (including band *18q22.3* or *18q23*) and not in patients with more proximal 18q deletions. [13]

In another study performed in Chromosome 18 Clinical Research Center at the University of Texas Health Science Center at San Antonio. Twenty-four participants (63%) had high-frequency hearing loss, similar to the pattern seen in presbycusis. Comparison of microarray results allowed identification of eight genes, including the candidate gene for dysmyelination (MBP). [13-14] our patient does not have hearing impairment or loss.

When using **MRI** dysmyelination is a common finding in people with distal 18q-, present in about 95%. Hypoplasia of thecorpus callosum is also a common finding. [11-12-15], our patient had no brain abnormalities on MRI.

Several people with distal 18q- have been diagnosed with low IgA levels, resulting in an increased incidence of infections. [11-12-15]

97% of individuals possess some form of mental retardation, ranging from moderate to severe cases.The intellectual development of individuals with de Grouchy syndrome vary quite widely. In one study of 46 individuals with this syndrome, IQ ranged from 49 to 113, with most individuals falling in the mild to moderate range of intellectual disability. Some of those with IQ scores on the lower end of the spectrum probably actually had deletions encompassing the *TCF4* gene. [10]

An increased incidence of autism is seen within the de Grouchy syndrome population. In a recent study, 45 of 105 individuals evaluated fell into the "possible" or "very likely" levels of risk for autism.Adaptive skills may also be delayed in people with the syndrome .[9-10-15]

At present, treatment is symptomatic, meaning the focus is on treating the signs and symptoms of the conditions as they arise. To ensure early diagnosis and treatment, people with de Grouchy syndrome are suggested to undergo routine screenings for thyroid, hearing, and vision problems. [10-15]

In one study,the ocular findings in one patient with 46, XX, del 18 (q21) consisted of hypertelorism, epicanthus, strabismus, myopia, microphthalmia, microcornea, corneal opacities, iris hypoplasia with full thickness defects, corectopia and large peripapillary staphylomata. The second patient with 46, XX, del (18) (pter --->q21.2: q22 -->qter), inv (21) (q21 -->p12: q21 -->qter) only had epicanthus, strabismus, myopia and peripapillary crescents. Based on the findings in these two patients and on a review of previously reported patients with del 18 qter it appears that the loss of band 18q23 may be responsible for malformations of the anterior segment in the 18q-syndrome. [16] .our patient suffered only from deeply settled eyes and partial ptosis.

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A study of a patient with 18p monosomy and GH deficiency due to pituitary hypoplasia, who showed an excellent response to GH-treatment, is described. Patients with this syndrome should be considered for endocrine evaluation, as they can benefit from hormonal substitution. [16, 17],our patient even though she had a normal pituitary gland anatomy, she had no improvement when treated with G.H. therapy.

Conclusion

It is important to report such cases in the literature as the clinical presentation of these cases are quite variable. It is imperative to do detailed chromosomal analysis in such patients to delineate 18p deletions from other syndromes with similar clinical presentation and to detect the extent of deletion as management may vary with the amount of chromosomal loss.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient's mother has given her consent for the child images and other clinical information to be reported in the journal. The mother informed that the patient's names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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