Cytogenetic and Clinical Description of Maternally Inherited Pure Trisomy 4p

Original Article

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ABSTRACT

Background: Trisomy 4p is a rare constitutional chromosomal rearrangement that leads to severe intellectual disability, characteristic facial features including a characteristic nose with a flat bridge and a bulbous tip (boxer nose), and extremities abnormalities. Pure trisomy 4p syndrome is due to duplication of the entire p arm of chromosome 4. Genotype-phenotype correlations in pure trisomy 4p cases are not well understood. Only five cases of pure trisomy 4p was previously reported in form of iso 4p, derivative formation and marker formation.

Aim: Here, we present the clinical and laboratory findings of fifth case of pure trisomy 4p with interesting MRI manifestations.

Results: Our patients' karyotype was defined as 47,XY,+(4)(pter→q11) mat that was inherited from his mother who had balanced translocation defined as 46, XX, t(4;12)(q12;q24.33).

Conclusion: Our case is the sixth case of pure trisomy 4p and the 2nd report of pure trisomy 4p due to the presence of marker. Our findings emphasize and strengthen the clinical features of patients with pure trisomy 4p and add to few reported cases. More accurate clinical reports of patients with pure trisomy 4p is needed for more elucidation of the pathogenesis of pure trisomy 4p syndrome.

Key Words: 4p chromosomal rearrangement, FISH analysis, MRI manifestations.

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INTRODUCTION

Chromosome gain is harmful to embryogenesis. Embryos with autosomal trisomies rarely survive and always have many pathological abnormalities (**Krivega *et al.,* 2022**). Trisomy 4p is a rare constitutional chromosomal rearrangement that leads to severe intellectual disability, characteristic facial features including flat nasal bridge and a bulbous tip (boxer nose), and extremities abnormalities. Mostly, 4p trisomies are inherited from familial balanced translocations, however it may occur sporadically (**Dallapiccola *et al.,* 1977; Gonzalez *et al.,* 1977; Demirhan *et al.,* 2010**). The severity of the disease depends on the size and location of the duplication and genes involved as well as the associated deletions. The characteristic manifestations of 4p trisomy are probably due to duplication of 4p15.2 -p16.3 (**Wyandt *et al.,* 1993; Karmous-Benailly *et al.,* 2005; Bartocci *et al.,* 2008; Demirhan *et al.,* 2010**).

Pure trisomy 4p syndrome is due to duplication of the entire p arm of chromosome 4. However, most of the reported cases are either partial or nearly pure trisomy 4p that are associated with other chromosomal deletions and commonly are the result of unbalanced segregation of inherited translocations forming derivatives. However, pure trisomy 4p was very rarely described and caused by isochromosome formation secondary to a de novo whole arm translocation (**Patel *et al.,* 1995; Pota *et al.,* 2014; Nasri *et al.,* 2024**). Genotype-phenotype correlations in pure trisomy 4p cases are not well understood. Determining the origin of the phenotypes observed in cases with extra chromosomes is important for understanding the molecular basis of trisomy syndromes (***Yao et al., 2022***).

Here, we present the clinical and laboratory findings of the sixth case of pure trisomy 4p with interesting MRI manifestations.

Ethics approval and consent to participate

The study was approved by the ethical committee of the National Research Centre, Egypt (6-2023/2-2-6), which follows the ethical standards of the Declaration of Helsinki.

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All participants gave informed written consent before their inclusion in the study.

Clinical Report

An 8-year-old boy was referred to the clinical Genetics department at the National Research Centre, Egypt for the evaluation of developmental/intellectual delay and skeletal deformities. He was the 2nd child of a non-consanguineous parents. His mother suffered from delayed speech. He had dysmorphic features in the form of long face, microcephaly/plagiocephaly, upward slanting of the eyes, hypertelorism, thin outer third of the brow, long phlitrum, thin upper lip, broad nose, pointed Chin, deformed posterior rotated ears and short neck. He had right claw clinched hands (compatodactyly). He also had right talipes which was operated upon and had overriding of the 2nd toe. He suffered from costo-vertebral dysplasia and scoliosis. He had a history of convulsion twice at the age of 8. He was hyperactive and showed abnormal movement in the form of self-biting. His brain MRI showed mild ventriculomegaly, absent splenium of corpus callosum, enlarged 4th ventricle, mild vermis hypoplasia and unilateral cerebellar hypoplasia (Figure 1).

Laboratory investigations

Chromosomal study of the patient revealed 47,XY,+marker. Karyotype for the parents and siblings was done and revealed normal chromosome complement for the father and the brother. However, the mother showed 46,XX,t(4;12)(q12;q24.33). Accordingly, the patient karyotype was defined as 47,XY,+(4)(pter→q11) mat.

FISH was done using locus-specific probe for Wolf-Hirschhorn syndrome (4p16.3), labelled in red and combined with a 4qter subtelomere specific probe, labelled in green as a control (Cytocell, Oxford gene technology Cambridge, UK). It confirmed the G banding results (Figures 2, 3).

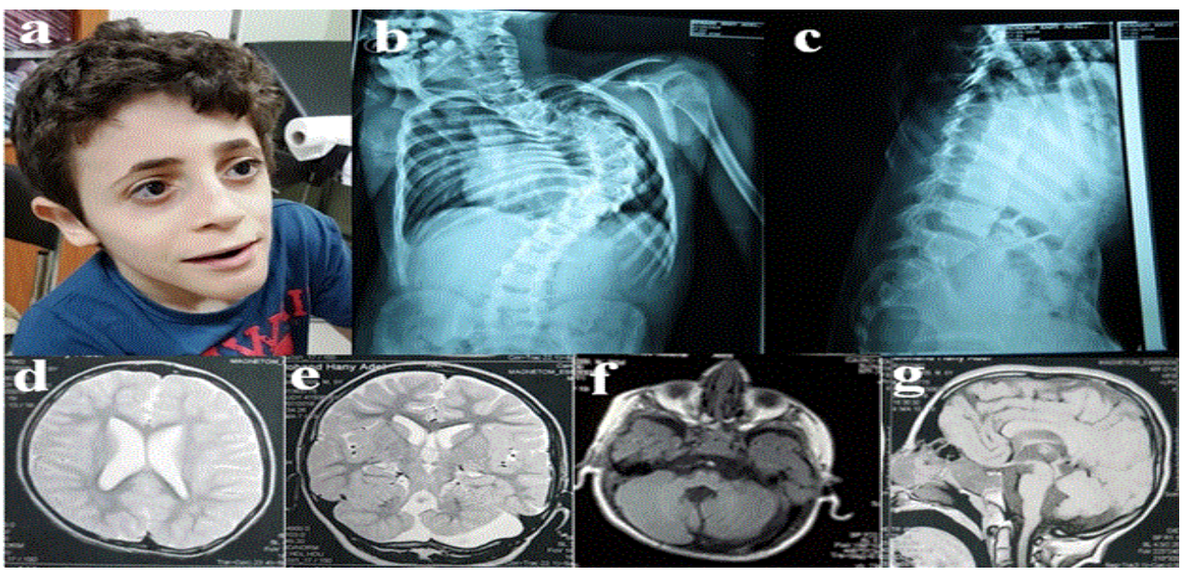

Figure 1: a. The patient's facial feature. b. and c. Chest X ray is showing scoliosis. d, e, f and g. MRI is showing mild ventriculomegaly, absent splenium of corpus callosum, enlarged 4th ventricle, mild vermis hypoplasia and unilateral cerebellar hypoplasia.

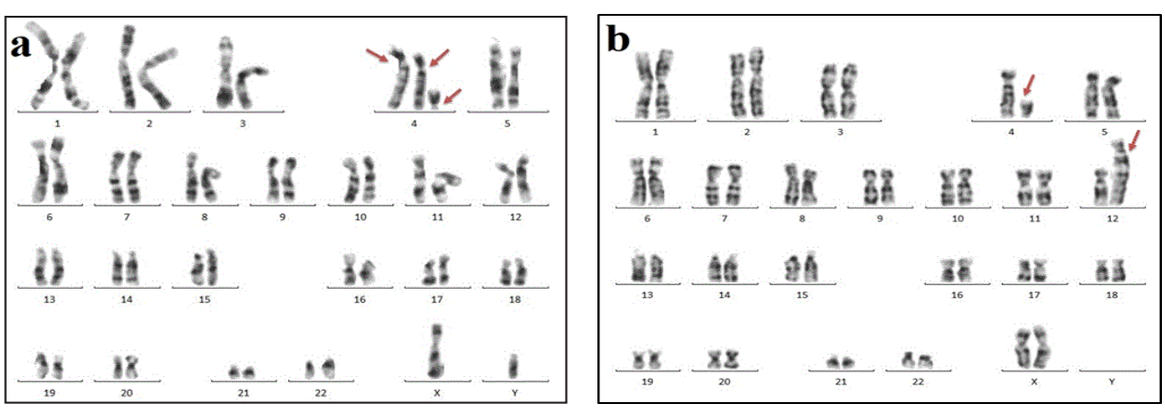

Figure 2: karyotypes of a. the patient showing 47,XY,+4p. b. the mother showing 46, XX, t(4;12)(q12;q24.33).

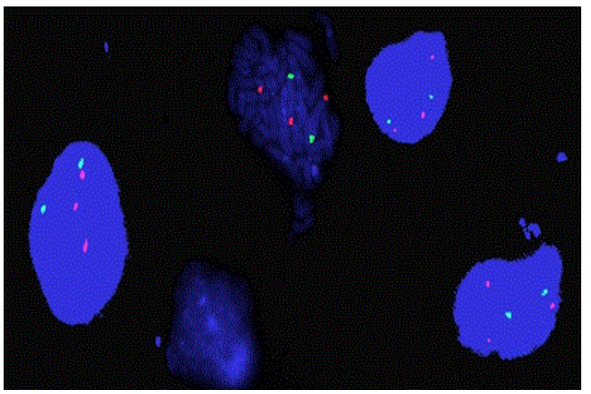

Figure 3: FISH analysis using Wolf-Hirschhorn FISH probe, (4p16.3) red and (4qter) green confirmed trisomy 4p.

DISCUSSION

An extra copy of 4p leads to a range of symptoms, including specific facial features, trouble breathing and eating, bone deformities, and hands and feet abnormalities. Children with trisomy 4p can be born with birth defects, such as abnormalities of the heart, kidney, brain, and genitals. They are usually small at birth and remain smaller than their peers, and manifest severe intellectual disability (ID). Partial 4p trisomy is associated with characteristic various congenital anomalies/ID syndrome with clinical manifestations that include the characteristic flattened nasal bridge, bulbous nose, abnormal ears, and flexion contractures (**Dallapiccola *et al.,* 1977; Gonzalez *et al.,* 1977; Wyandt *et al.,* 1993: Bartocci *et al.,* 2008**). The clinical manifestations of our patient appears to coincide with the reported trisomy 4p clinical pictures.

Ultrasound of the brain of a case with Pure Trisomy 4p due to iso 4p, showed brain malformations in form of agenesis of the septum pellucidum and interconnected frontal horns and lateral ventricles. Moreover, the ultrasound showed normal corpus callosum and minor dilatation of the lateral ventricles (**Zahed *et al.,* 2004**). This coincides with our patient who showed also brain malformations in form of mild ventriculomegaly, absent splenium of corpus callosum, enlarged 4th ventricle, mild vermis hypoplasia and unilateral cerebellar hypoplasia.

The inconsistency in the extent of the reported trisomic segment makes it hard to recognize a pure trisomy 4p syndrome. Yet, the clinical manifestations of our patient appears to coincide with the reported trisomy 4p clinical pictures. Moreover, hypoplasia of the 12th rib and agenesis of the septum pellucidum are considered as unique features of pure trisomy 4p due to iso 4p (**André *et al.,* 1976; Zahed *et al.,* 2004**). Our patients showed costo-vertebral dysplasia and absent splenium of corpus callosum.

As far as to our knowledge, only five cases of pure trisomy 4p were previously reported in form of iso 4p (**André *et al.,* 1976; Zahed *et al.,* 2004; Pota *et al.,* 2014**), derivative formation (**Patel *et al.,* 1995**) and marker formation (**Dallapiccola *et al.,* 1977**). Our cases is the 2nd case of pure trisomy 4p due to marker formation. Both cases are maternally inherited. The following table demonstrates the clinical manifestation of the previous reported cases of pure trisomy 4p compared to our patient (Table 1).

In addition, we compared the clinical manifestations of our patient with the previously described cases of different chromosome 4p rearrangements resulting in trisomy 4p, in the form of recombinant chromosome 4 and trisomy 4p (either partial or pure) (Table 2). Recombinant chromosome 4 arises from pericentric inversion leading to a duplicated segment of 4p13~p15→4pter. (**Patel *et al.,* 1995; Schinzel, 2001; Garcia-Heras *et al.,* 2002; Mun *et al.,* 2010; Gardner *et al.,* 2012; Hemmat *et al.,* 2013**).

Most of the reported trisomy 4p were due to inherited chromosomal translocations, commonly involving chromosome 22 (**Zahed *et al.,* 2004**). However, our patients inherited the abnormality from his mother who had translocation involving chromosome 12, t(4;12).

Genotype-phenotype evaluations helps to recognize genes involved in the pathogenesis of genetic syndromes. As mentioned before, only five cases of pure trisomy 4p was previously reported in form of iso 4p (**André *et al.,* 1976; Zahed *et al.,* 2004; Pota *et al.,* 2014**), derivative formation (**Patel *et al.,* 1995**) and marker formation (**Dallapiccola *et al.,* 1977**). Our case is the sixth case of pure trisomy 4p and the 2nd report of pure trisomy 4p due to the presence of marker. Our findings emphasize and strengthen the clinical features of patients with pure trisomy 4p. More accurate clinical reports of patients with pure trisomy 4p is needed for more elucidation of the pathogenesis of pure trisomy 4p syndrome.

DECLARATIONS

Availability of data and materials

All data generated or analyzed during this study are included in the manuscript.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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Table 1: Demonstrates the clinical manifestations described in previous reported patients of pure trisomy 4p compared to our patient:

Clinical Manifestations	Our patient	Dallapiccola *et al.*, 1977	Patel *et al.*, 1995	Pota *et al.*, 2014	Zahed *et al.*, 2004
The abnormality	marker	marker	der t(4,22)	iso 4p	iso 4p
origin	maternaly inherited	maternaly inherited	de novo	de novo	de novo
Sex	male	male	female	male	female
Full gestational period	+	NAD	+	+	+
Growth retardation	+	+	+	+	+
Microcephaly	+	+	-	+	+
Eye anomalies	-	NAD	+	+	-
Bulbous nose	+	+	+	+	+
Retro-/micrognathia	-	NAD	+	+	-
High-arched palate	+	+	+	-	+
Ear anomalies	+	+	+	+	-
Short neck	+	+	+	+	+
Widely spaced nipples	-	NAD	+	+	+
Vertebral/rib anomalies	+	+	+	+	+
Upper Limb anomalies	+	+	+	+	-
Lower Limb anomalies	+	+	+	-	+
Brain abnormalities	+	NAD	+	+	+
Heart defects	-	NAD	-	+	+
Psychomotor retardation	+	+	+	+	+

Table 2: Clinical manifestations of our patient and the previously reported cases of different chromosome 4 rearrangements:

		Our patient	Recombinant Chr 4	Trisomy 4p
Growth retardation		+	+	+
Facial features	Microcephaly	+	+	+
	Abnormal ears	+	+	+
	Thin upper lip	+	+	+
	Broad nose	+	+	+
	Pointed Chin	+	+	+
Short neck		+	+	+
Broad chest		+	+	+
Cardiopathy		-	+	-
Urogenital abnormality		-	+	-

AUTHORS' CONTRIBUTIONS

OE, ME, RK: conducting the laboratory work, participating in writing the manuscript and preparing the paper for submission.

GA: Clinical evaluation, case follow up, collection of the samples, participating in writing the manuscript and preparing the paper for submission.

All authors have read and approved the manuscript.

CONFLICT OF INTEREST

There are no conflicts of interest.

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