Oculodentodigital dysplasia with massive brain calcifications and a new pathogenic mutation

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BACKGROUND

Oculodentodigital dysplasia (ODDD) [MIM 164200] is a rare autosomal dominant disorder caused by mutations in the gap junction alpha 1 (GJA1) gene, on chromosome 6, encoding for connexin 43 (Cx 43). Typical signs include type III syndactyly of the fourth and fifth finger, microphtalmia, microcornea, short palpebral fissures, microdontia, enamel hypoplasia and neurological disturbances (spastic paraparesis, ataxia, neurogenic bladder dysfunction and occasionally mental retardation).

CASE REPORT

We report a 59 year old man, observed for progressive gait disturbances and unsteadiness, presenting since birth bilateral type III syndactyly of the third, fourth and fifth finger (surgically corrected) and bilateral syndactyly of second and third toe. Decreased visual acuity with glaucoma and cataracts, microdontia, caries and teeth loss were evident since childhood. Clinical examination showed the classical ODDD features. From the neurological point of view, blindness, unsteadiness and spasticity of inferior limbs were present. A computerized tomography (CT) scan revealed gross calcifications of basal ganglia and cerebellar nuclei. Magnetic resonance imaging showed a thin corpus callosum, mildly enlarged ventricles and leucoencephalopathy. Phosphorus and calcium metabolism examination, including parathormone, was normal.

The clinical findings suggested ODDD, with some atypical features rarely reported (massive brain calcifications).

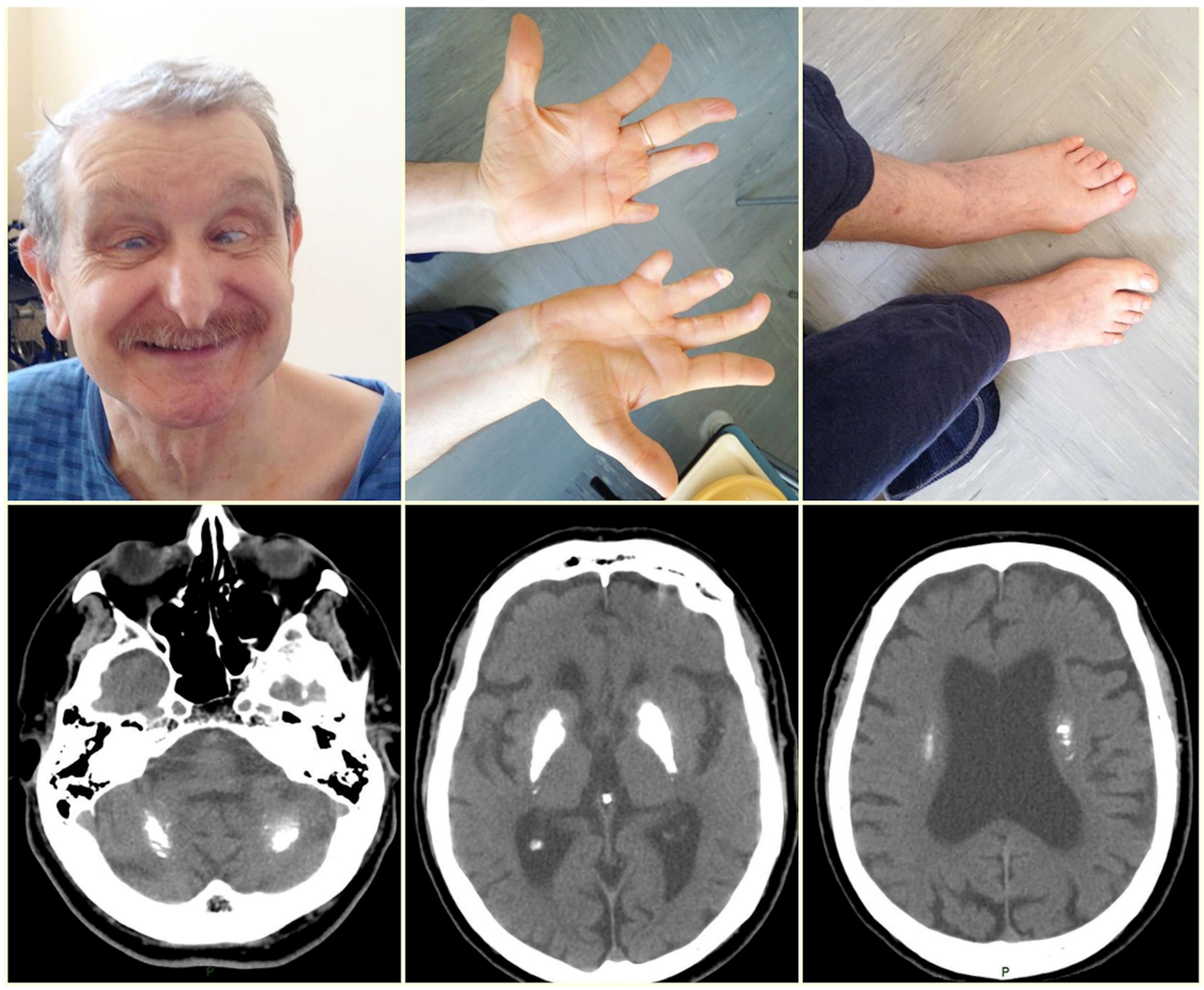

Figure 1. Upper row: Morfological manifestations of ODDD in the patient. Lower row: Brain CT scan showing gross bilateral calcifications of basal ganglia and cerebellar nuclei and a tetraventricular enlargement.

Mutation analysis

Sequence analysis of the *GJA1* gene disclosed a heterozygous missense mutation [NM_000165.3:c.124G>C;p.(Glu42Gln)] altering an amino-acid residue highly conserved across multiple species, including chimpanzee, macaca, dog, cows, mouse, rat, chicken, xenopus and zebrafish. The identified mutation was never previously reported and, according to bioinformatical studies, resulted pathogenic. Specifically, the p.(Glu42Gln) mutation alters the last amino-acid residue of the first transmembrane domain (TM1) of Cx43, at the boundary with the first extracellular loop domain.

Homo sapiens	1	MGDWSALGKLLDKVQAYSTAGGKVWLSVLFIFRILLLGTAV**E**SAWGDEQS	50
Pan troglodytes	1	MGDWSALGKLLDKVQAYSTAGGKVWLSVLFIFRILLLGTAV**E**SAWGDEQS	50
Macaca mulatta	1	MGDWSALGKLLDKVQAYSTAGGKVWLSVLFIFRILLLGTAV**E**SAWGDEQS	50
Canis lupus familiaris	1	MGDWSALGKLLDKVQAYSTAGGKVWLSVLFIFRILLLGTAV**E**SAWGDEQS	50
Bos taurus	1	MGDWSALGKLLDKVQAYSTAGGKVWLSVLFIFRILLLGTAV**E**SAWGDEQS	50
Mus musculus	1	MGDWSALGKLLDKVQAYSTAGGKVWLSVLFIFRILLLGTAV**E**SAWGDEQS	50
Rattus norvegicus	1	MGDWSALGKLLDKVQAYSTAGGKVWLSVLFIFRILLLGTAV**E**SAWGDEQS	50
Gallus gallus	1	MGDWSALGKLLDKVQAYSTAGGKVWLSVLFIFRILLLGTAV**E**SAWGDEQS	50
Danio rerio	1	MGDWSALGRLLDKVQAYSTAGGKVWLSVLFIFRILVLGTAV**E**SAWGDEQS	50
Xenopus tropicalis	1	MGDWSALGRLLDKVQAYSTAGGKVWLSVLFIFRILLLGTAV**E**SAWGDEQS	50

Table 1. Alignment of amino acid residues adjacent to Cx43 p.(Glu42Gln) mutation showing high level of conservation among different species. The amino acidic residue altered by the mutation is written in red.

CONCLUSIONS

The presence in our patient of many phenotypic features of the disease (face, eye, teeth and digits involvement) led us to the diagnostic suspicion of ODDD. However, the evidence at the CT scan of massive bilateral calcifications is intriguing, since brain calcifications have been reported in a small proportion of ODDD patients. The presence of massive brain calcifications in ODDD may suggest that, in addition to the GJA1 functions reported so far, the gene could also have a role in the homeostasis of brain microvessels, its mutation leading to the deposition of calcium, similarly to what happens in Primary familial brain calcification. In conclusion, this case expands the knowledge of ODDD, with the evidence of a new *GJA1* mutation which may cause an alteration of the brain microvessels leading to massive calcifications.

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