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Neurological manifestations of the oculodentodigital dysplasia syndrome

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■ **Abstract** Oculodentodigital dysplasia (ODDD) (MIM 164200) is a rare autosomal dominant inherited disorder affecting the development of the face, eyes, limbs and dentition. Neurological complications are thought to be occasional manifestations of the disorder. This report illustrates the neurological manifestations by a pedigree of two ODDD patients with spastic paraparesis, cerebral white matter hyperintensity and basal ganglia hypointensity. A systematic review of the English, French, German and Italian literature on ODDD is also provided to summarize the neurological manifestations of the disorder. 243 previously described ODDD cases presented a spectrum of neurological manifestation including spasticity (25), subcortical

white matter lesions (9) and basal ganglia changes (6) on MRI. Additional findings consisted of gaze palsy and squinting (28), bladder and bowel disturbances (21), visual loss (20) and blindness (4), hearing loss (15), ataxia (11), nystagmus (9), muscle weakness (5) and paresthesias (3). Neurological manifestations, including spasticity associated with MRI changes, are an underrecognized feature in the ODDD phenotype. A clinical guide to the neurological manifestations of ODDD may assist in the assessment of patients with this condition.

■ **Key words** oculodentodigital dysplasia · white matter lesions · syndactyly

Introduction

In 1920, Lohmann [38] described two patients with a syndrome of microphthalmus and bilateral camptodactyly of the fifth finger. Thirty years earlier, Brailey [6] had described a syndrome with microphthalmia and abnormalities of the teeth, with no mention of syndactyly. Several descriptions of similar cases with incomplete features were published before 1957 [3, 4, 51, 71]. In that year, Meyer-Schwickerath et al. [40] introduced the term 'Dysplasia oculo-dento-digitalis' or ODDD, and in 1963, Gorlin et al. [26] summarized the 6 known cases and defined the syndrome.

Today, ODDD has a recognized constellation of

symptoms with an autosomal dominant inheritance pattern: a depressed nasal bridge, a thin nose with hypoplastic alae and thin, anteverted nostrils, microphthalmos with anomalies of the iris and microcornea, syndactyly and camptodactyly of the fourth and fifth digits, and hypoplasia of the tooth enamel (Table 1) [8, 9, 19, 21, 23, 26, 32, 49, 58, 68, 70].

Recently, the location of the gene for ODDD was narrowed to a 1-centimorgan interval [5] on chromosome 6q [25]. In a few reports, affected individuals developed spastic paraparesis, quadriplegia, gait disturbance, bladder disturbances, and hyperreflexia [29, 44, 48, 59]. Cerebral white matter abnormalities identified by magnetic resonance imaging (MRI) have been proposed as the cause of these neurological symptoms [27, 29, 45, 59,

Table 1 Clinical manifestations of ODDD

Ophthalmological manifestations
<ul style="list-style-type: none"> • Microphthalmia with small sunken eyes • Microcornea • Malformations of the iris • Glaucoma • Optic atrophy
Dental manifestations
<ul style="list-style-type: none"> • Enamel hypoplasia, resembling amelogenesis imperfecta • Microdontia • Missing teeth and premature loss of teeth • Caries
Malformations of hands and feet
<ul style="list-style-type: none"> • Bilateral syndactyly of the fourth and fifth fingers (type III syndactyly) • Midpharyngeal and distal pharyngeal hypoplasia or aplasia of digits or toes • Camptodactyly and clinodactyly of the fifth fingers
Craniofacial manifestations
<ul style="list-style-type: none"> • Epicanthic folds • Short palpebral fissures • Hyper- or hypotelorism • Narrow nose with hypoplastic alae and a long nasal bridge • Thin anteverted nostrils • Wide alveolar ridge • Cleft lip and palate • Cranial and mandibular hyperostosis • Microcephalus
Skeletal manifestations
<ul style="list-style-type: none"> • Broad tubular bones • Cubitus valgus • Hip dislocation • Osteopetrosis
Hair manifestations
<ul style="list-style-type: none"> • Fine, dry, thin, sparse, slow growing hair (hypotrichosis)

Neurological manifestations (see Table 2)

61]. However, this connection has not been systematically investigated, and MRI is still not routine in the evaluation of ODDD patients.

We describe a pedigree of 2 ODDD-patients (mother and son) with spastic gait associated with leukodystrophic changes visible on MRI, and we review the literature on the neurological manifestations of ODDD and the results of brain imaging in these patients.

Case reports

■ Case 1

A 63-year-old right-handed woman was admitted for evaluation of progressive unsteadiness of gait. She had

lifelong trouble with her teeth and lost her last tooth at the age of 33 years. She had suffered from diarrhea and malabsorption beginning at age 34 and underwent subtotal colectomy 8 years later because of polyposis coli. Relapsing middle ear infections in the late 1970s caused hearing loss in the right ear. Bilateral glaucoma was diagnosed in 1990. Because of increasing unsteadiness of gait over the last five years she was referred to our clinic where ODDD was first diagnosed. General examination revealed bilateral syndactyly of the fourth and fifth fingers (Fig. 1 A, B). Cranial nerve examination showed bilateral ptosis (Fig. 1 C) and conductive hearing loss in the right ear. Motor examination revealed spastic paraparesis, lower limb hyperreflexia, and pronounced scissor gait. She had normal plantar reflexes but displayed gait ataxia, dysmetria of the arms and legs, dysarthria, and high-pitched speech. She also reported sensory loss on the left side of the trunk. Neuropsychological testing revealed deficits in verbal learning, short-term memory, visuospatial tasks, and an attention deficit. Her IQ was assessed at 79.

The right corneal diameter was 11 mm and the left was 10 mm. The interpupillary distance was 57 mm. Ocular abnormalities included a beginning bilateral cataract and a mildly raised intraocular pressure of 20 mm Hg in both eyes. Pupils reacted normally to light. Visual acuity was 0.8 on the right and 0.6 on the left. Funduscopy was unremarkable.

■ Clinical investigations

Biochemical evaluation for leukodystrophy syndromes showed no signs of adrenoleukodystrophy, metachromatic leukodystrophy, or globoid cell leukodystrophy. Plasma amino acids, hexosaminidase A and B, routine blood and CSF findings were all normal.

Muscle responses upon electromagnetic transcranial stimulation of the motor cortex were obtained from the abductor pollicis brevis and the anterior tibial muscle. They showed no cortical response but normal peripheral latencies. Somatosensory evoked potentials of the median nerve were normal. Latencies of the left tibial nerve were delayed while the right side was within normal range. Visual evoked potentials were normal and did not suggest optic neuropathy. An audiogram found conductive hypacusis in the right ear. Cranial CT showed bilateral subcortical hypodense lesions in the insula. Brain MRI showed diffuse abnormal high signal intensity of the subcortical white matter in T2-weighted images bilaterally. By contrast, the signal was low in the cortex, in particular in the precentral region. Furthermore, the signal intensity of the basal ganglia in the spin echo-sequences images was lowered (Fig. 3 A). An MRI of the spine was normal.



Fig. 1 (A) Palmar and (B) dorsal view on the hands of patient 1 demonstrates bilateral syndactyly of the fourth and fifth finger (syndactyly type III). (C) 63-year female with typical facial features of ODDD including small sunken eyes, small palpebral fissures, hypotelorism, hypoplastic nasal alae and mildly anteverted nostrils.

■ Case 2

The son of the first patient, a 35-year-old construction-worker, also had bilateral syndactyly of the fourth and fifth finger, enamel hypoplasia, and facial abnormalities typical of ODDD. No other family members with symptoms suggestive of ODDD are known. At age 10, he began experiencing unsteadiness of gait and stiffness of the legs. He had the syndactyly of the right hand surgically corrected at age 29.

The function of the cranial nerves was normal, except for a saccadic gaze. He had a spastic tetraparesis with enlarged reflex zones, a pronounced scissor gait, and lower limb hyperreflexia. Foot and patellar clonus were present. Finger-nose testing was dysmetric bilaterally. No sensory deficits were noted.

MRI of the brain showed diffusely abnormal high signal in the subcortical white matter (Fig. 3 C).

Review of the literature

To our knowledge, 243 cases of ODDD have been reported. Because most of the articles were written by specialists with limited interests, the reported incidence of neurological deficits may be misleadingly low. A summary of reported neurological symptoms in these cases is given in Table 2.

■ Neurological symptoms in the medical history

Additional neurological symptoms in these patients' medical history are glaucoma [7, 14, 36, 40, 46, 57, 61, 71], headache, most likely due to glaucoma [40, 53, 57], migraine [45], epilepsy [34, 48, 60, 61], nonspecific encephalopathy [42], encephalitis [17], fecal incontinence [45], tinnitus [53], and hyperactivity treated with amphetamines [32].

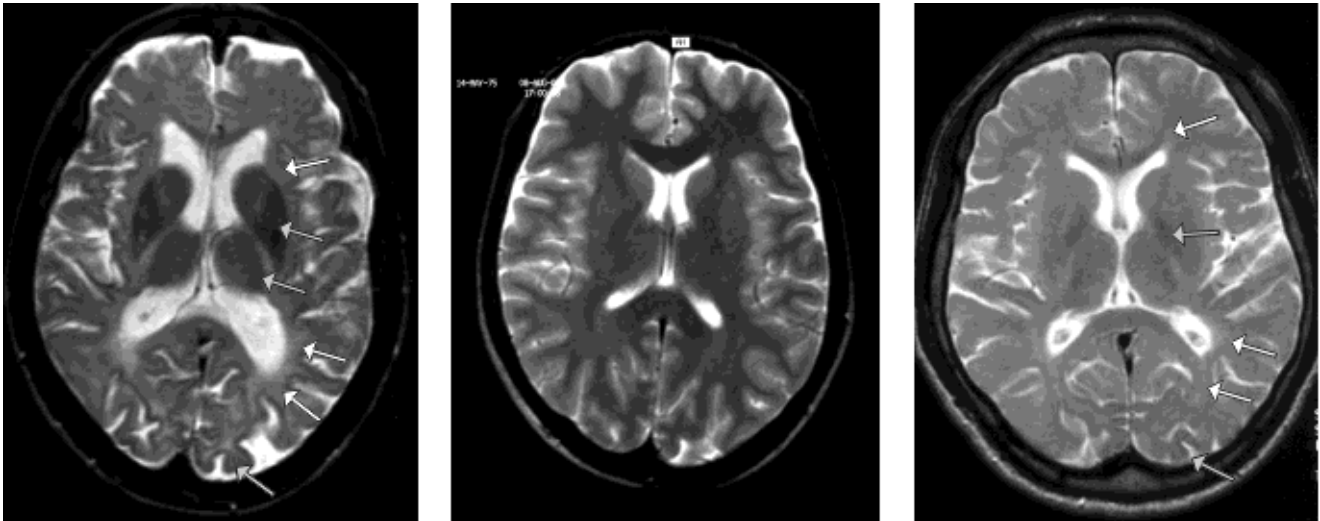


Fig. 2 (A) An axial spin-echo sequence image (TR 4000/TE 90/TA 2:28) of case 1 demonstrates hypointensity of the cortex, caudate nucleus and the thalamus (grey arrows), periventricular white matter hyperintensity, particularly pronounced in the occipital lobes (white arrows) as well as mild cerebral atrophy in the same plane as figure 4. (B) Axial spin-echo sequence image (TR 4000/TE 90/TA 2:28) of a normal person in the same plane as fig. 1A and 1C. (C) The axial T2-weighted image of case 2 (TR 2700/TE 90/TA 8:42) shows periventricular leukodystrophic changes (white arrows) and hypointensity in the basal ganglia and the occipital cortex (grey arrows).

■ Cranial nerves

Visual and hearing impairment is common. Reported abnormal findings in the cranial nerves frequently include reduced visual acuity [14, 19, 16, 17, 28, 30, 36, 44, 48, 55, 57, 61, 63, 69], visual field loss [40, 63] and a history of visual loss [6, 14, 47, 71]. Even one case of anophthalmia [22] and four cases of blindness (most likely due to glaucoma) [2, 10, 14] have been reported. Some cases of visual impairment have been attributed to glaucoma [36], amblyopia [19, 46, 57, 71], and hypertension [8]. Abnormalities on funduscopy include optic atrophy [10], an increase in disc vessels [32], remnants of the hyaloid system [67, 71], and retinal hemorrhages as well as visual impairment most likely due to hypertension [8].

Impairment of eye movements includes squinting and gaze palsy [2, 10, 13, 16, 28, 51, 55, 73], strabismus [42, 46, 49], intermittent deviation of both eyes [67], intermittent double vision [53], oculomotor square wave jerks [59], and esotropia [32, 67, 69]. Bilateral ptosis [55] and nystagmus have also been described [2].

Hearing loss was reported in 15 patients; 11 conductive [8, 15, 26, 32, 45, 49, 53, 55, 65, 66], one central [48], and three not reported [2, 38, 45]. Normal hearing was present in at least four cases [2, 45, 64, 73].

■ Motor system

A common finding is spasticity [2, 48, 57], including spastic paraparesis [29, 44, 45, 48, 59], spastic diplegia [17], and spastic tetraparesis [1, 24]. Brisk reflexes [11, 29, 53] and pathological reflex signs [24, 29, 53, 57, 60]

were noted in several patients, but others had normal muscle tone and reflexes [69], hypotonia of the limbs [42], or even absent knee and ankle jerks [37]. Relatively uncommon findings include general muscle weakness [27], tibial muscle weakness [11], tremor [59], ataxia, in particular an ataxic gait [11, 17, 53, 59], dysdiadochokinesia [63], and dysmetria in finger-to-nose and heel-to-skin testing [53]. Dysarthria has been reported in four cases [11].

■ Sensory system

Sensory deficits are rare. Only one patient with pain in the lower limbs [45] and three patients with paresthesias have been described in addition to our case [1, 24, 27].

■ Autonomic system

Bladder disturbance has been reported frequently [1, 24, 44, 48, 57, 59], but bowel disturbance [24, 44, 45] and chronic diarrhea [36, 66] are more rare.

■ Neuropsychological deficits

Several authors have reported normal results on psychological testing [4], normal mental development [49, 55, 56, 64, 67], and normal intelligence [2, 10, 26, 31, 35, 44, 50, 52, 53, 56, 65, 69], but others have reported reduced intelligence [45, 60, 63, 65, 73] and mental retardation [19, 31, 33, 58]. One patient had a speech defect [26]. Sim-

Table 2 Systematic review of neurological symptoms in previously reported patients with ODDD

Cranial nerves	cases
Gaze palsy/squinting	28
Decreased visual acuity and visual loss	20
Loss of hearing	15
• conductive	11
• central	1
• unknown (central/conductive)	3
nystagmus	9
Abnormalities on funduscopy	6
• increase in disc vessels	3
• remnants of the hyaloid system	2
• retinal hemorrhages	1
blindness	4
Visual field defects	3
anophthalmia	1
bilateral ptosis	1
oculomotor square waves	1
Motor system	cases
spasticity	25
• no detailed description	4
• spastic paraparesis	16
• spastic paraplegia	1
• spastic tetraparesis	2
• increased reflexes	7
• reported pathological reflex signs	5
ataxia and atactic gait	11
muscle weakness	5
dysarthria	4
tremor	2
hypotonia	1
dysdiadochokinesia	1
normal muscle tone and reflexes	1
dysmetria	1
Sensory system	cases
paraesthesias (in the legs)	3
pain in the lower limbs	1
Autonomic system	cases
bladder disturbance	18
bowel disturbance	3
chronic diarrhea	2

ilarly, Zach reported that these patients have a relatively low verbal IQ [73].

■ Neurophysiological and laboratory investigations

Gillespie found generalized slowing in the EEG of one patient [23], which is similar to the slowing in our patient. Another patient with bilateral occipital slowing in EEG and epilepsy has been reported [61]. One patient with epilepsy presented with a focus on the EEG [60]. Ten patients with a normal EEG have been reported [1, 17, 22, 23, 34, 44, 48, 53, 63].

Table 2 *continued*

Neuropsychological status	cases
normal intelligence and development	22
Reduced intelligence	5
Retarded	4
Investigations	cases
EEG	13
• normal	10
• generalized slowing	2
• focus	1
prolonged latency in VEP	10
CSF	5
• normal	4
• elevated protein in CSF	1
abnormal ERG	3
Audiogramme	3
• abnormal	2
• normal	1
prolonged latency in BAEP	1
Imaging	cases
MRI brain	10
• white matter changes	9
• normal white matter	1
• basal ganglia changes	6
• cortex abnormalities	4
Pneumoencephalographies	6
• abnormal	4
• Normal	2
CT-scans brain	5
• calcifications of basal ganglia	2
• normal cerebral structures	2
• cerebral atrophy	1
MRI spine	5
• spinal chord atrophy	4
• normal	1
Myelographies	2
• spinal chord atrophy	1
• normal	1

In a study of 9 patients, all had prolonged latency of visual evoked potentials [48]. Prolonged VEP latencies and prolonged BAEP latencies were found in one individual [29]. No abnormalities were found in nerve conduction studies [1, 44, 59] and EMG [1, 59].

Abnormal responses in the electroretinogram have been documented in three patients [42, 47, 63]. An audiogram was performed in three patients, with abnormal findings in one [35, 63]. Elevated protein in CSF was found in one case [48], but investigation of the CSF was normal in four other patients [1].

■ Imaging

Sörgel and Heidrich [60] were the first to describe enlarged ventricles on pneumoencephalography. Thoden et

al. [65] described a four-month-old child with ODDD and found cerebral atrophy on pneumencephalography. No evidence of cortical atrophy was seen by Farman et al. [17], who found ventricles on the upper limit of normal size on air encephalography. Normal pneumencephalography was reported by Cowan in 1959 [10]. Tomodensitometry of the brain was normal in two cases [1, 44], but another study of brain CT revealed bilateral dense calcification of the basal ganglia and mild hydrocephalus [2]. Some investigators also described a widening of the bones at the base of the skull on CT [67], cerebral atrophy [24], or a normal brain CT [61].

MRI of the brain has been reported in 10 patients [24, 27, 29, 45, 57, 59, 61]. Gutmann et al. [29] were the first to report abnormal cerebral white matter findings in a 21-year-old woman with progressive spastic paraparesis and suggested that the description of the phenotype of ODDD should be expanded to include spastic paraparesis. Norton et al. [45] ascribed the spasticity to white matter lesions, and proposed an expansion of the phenotype to include spastic paraparesis due to leukodystrophic changes. Abnormally high white matter intensity on T2-weighted images in nine cases [24, 27, 29, 45, 59, 61] was particularly marked in the periventricular parieto-occipital region [45, 59] and in the temporal lobe [61] extending to the midfrontal region [45], extending to the posterior limbs of the internal capsule [24] and extending down to the corticospinal tracts [27] and inferiorly to the medulla [29]. No white matter lesions were found in one case, although basal ganglia changes were present [57]. In addition to these leukodystrophic changes, other findings included signal hypointensity in the globus pallidus, substantia nigra, red nucleus [24, 27, 29, 57], and thalamus [29]. Also, signal hypointensity was found in the cortex [27], in particular the parietooccipital region [24]. This signal hypointensity is thought to be consistent with iron deposition [29, 57, 61]. The clinical presentation associated with MRI changes of the brain includes spastic paraparesis and sphincter disturbances [24, 29, 45], tremor [59], progressive paresthesias, decreased proprioception [24, 27] and seizures [61]. One patient with normal neurological status and white matter abnormalities has been described [27].

Magnetic resonance images of the spine were normal in one case [29] and demonstrated mild spinal chord atrophy in four cases [24, 27]. Myelography revealed spinal cord atrophy in one case [2] and was normal in another [48].

Discussion

Although a variety of neurological symptoms have been described in patients with ODDD, only sporadic reports address neurological manifestations of the autosomal

dominant disorder in particular [45, 59]. Several reports completely neglect the neurological evaluation of ODDD patients [12, 21, 54, 66, 69, 72], while others evaluated only the neuro-ophthalmological features of the syndrome [7, 46]. However, in one report the neurological symptoms were so dominant that ODDD was not recognized, and hereditary spastic paraplegia with neurogenic bladder disturbances and syndactyly was diagnosed [48].

Because of the different interests of the authors of the previous reports, the exact prevalence of neurological symptoms in ODDD cannot be determined from the literature. Our literature search suggests that the core neurological presentations of ODDD include loss of visual acuity and hearing, spasticity, sphincter disturbances, gait ataxia, and abnormalities on MRI. An array of other neurological symptoms, such as bilateral ptosis, tremor, dysmetria, dysarthria, sensory loss, visuospatial deficits, and reduced intelligence, might depend on the variability of expression of the phenotype.

Changes of the subcortical white matter in MRI have been known since 1991 [29], and white matter lesions might predict the severity of the expression of the phenotype [59]. However, only 10 of 45 reported patients since 1991 have had MRI of the brain. We describe two additional patients with typical neurological manifestations of ODDD. In both cases, MRI showed hyperintensity of the subcortical white matter and hypointensity of the basal ganglia, the thalamus, and the cortex.

Our second patient developed spasticity and gait disturbance at a much younger age than his mother did. This supports the genetic anticipation observed by Shapiro et al. [59]. They observed that signs of the phenotype, e.g. leukodystrophy, tend to be expressed in a more severe form or appear at an earlier age of onset in subsequent generations suggesting a triplet repeat disorder [59]. The hypothesis of a suspected trinucleotide mutation is also supported by features similar to ODDD described in other triplet repeat disorders, such as spasticity [43], ataxia [20, 39], white matter changes on MRI [18] and morphological abnormalities of phalangeal development [41]. The triplet repeat in ODDD most likely affects a gene with impact on morphogenesis as well as on maintenance of cerebral function [59]. No pathology and no postmortem data has been reported so far in the reviewed 243 cases of ODDD, which could help in the search for the gene product responsible for ODDD. More than 40 genes and several diseases have been linked to the critical region for ODDD on chromosome 6q22–23 [5, 25]. Some of them also present with morphological malformations including metaphysial chondrodysplasia (Schmid type), spondylometaphysealdysplasia (Japanese type), rhizomelic chondrodysplasia punctata type I as well as syndactyly type III (<http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/getmap?chromosome=6q>). Among the genes in that region Bojadjev et

Table 3 243 previously reported ODDD cases

Author	Year	Cases	Age	Sex	Neurological symptoms	central nervous system radiographs
Brailey (teeth, microphthalmus)[6]	1890	1	18	f	loss of visual acuity	NR
Lohmann [38]	1920	2	10 6	f f	loss of hearing NR	Xray showed microcephalus and a narrowed base of the skull
Bauer (Syndactyly, facies) [3]	1927	2	NR	m	NR	NR
Wolff (microphthalmic family and abnormalities of the teeth) [71]	1930	5	NR	f f m m	reduced visual acuity, remnants of the hyaloid artery NR no light perception on right eye, glaucoma reduced visual acuity reduced visual acuity	NR
Berliner (microphthalmia and webbing of DIII and DIV) [4]	1941	2	5 1	NR f	psychologic tests showed normal mentality NR	NR
Pitter & Svejda [51]	1952	1	2	f	squinting	NR
Meyer-Schwickerath et al. [40]	1957	2	13 31	f m	visual loss and visual field narrowed, glaucoma visual loss, scotoma and headache due to glaucoma	NR
Cowan [10]	1959	1	16	m	optic atrophy, bilateral blindness, squinting, normal intelligence	normal pneumencephalography
Gorlin et al. [26]	1963	1	12	m	secondary speech defect, conduction hearing loss, IQ 108, Bender Gestalt test was normal	small calvaria on Xray of the skull
Littlewood & Lewis [37]	1963	2	7 NR	m m	absent knee and ankle jerks, Holmes-Adie syndrome NR	NR
Gellis & Feingold [21]	1964	1	NR	f	NR	NR
Gillespie [23]	1964	2	7 1	m f	EEG with slight generalized slowing EEG was normal, no change after photic stimulation	NR
Sörgel & Heidrich [60]	1965	1	7	f	epilepsy, focus in EEG, pyramidal tract signs, side-difference of reflexes, reduced intelligence, normal CSF	pneumencephalography showed enlarged ventricles, left greater right
Sugar et al. [63]	1966	1	20	f	EEG normal, IQ 80–90, reduced visual acuity, visual field narrowed, some dysdiadochokinesia, normal audiometry, abnormal ERG	NR
Rajec & De Veber [52]	1966	2	3 NR	f NR	no neurological defects, normal intelligence	NR
Kurlander et al. [34]	1966	1	1	f	generalized convulsions, normal EEG	Skull Xray showed poor ossification of the bones of the calvaria
Nguyen [42]	1967	1	NR	NR	encephalopathy and hypotonia of the limbs, strabismus, nystagmus, abnormal ERG	NR
Eidelman et al. [15]	1967	2	10 3	m f	bilateral conductive hearing loss NR	NR
Pfeiffer et al. [50]	1968	2	29 1	f m	normal intelligence, no nystagmus, visual fields unremarkable NR	Xray of the skull showed thickened Calvaria Xray of the skull unremarkable
Reisner et al. [53]	1969	4	14 7 6 33	m f m f	normal intelligence atactic gait, weakness, brisk reflexes, normal EEG conductive deafness, normal EEG, normal intelligence nystagmus, brisk reflexes, pyramidal signs, atactic gait, headache, tinnitus, double vision	hyperostosis in the infratentorial area of the skull on Xray hyperostosis of the skull/cranial vault
O'Rourke & Bravos [47]	1969	1	NR	m	decreased visual acuity, nystagmus, diminished response in an electroretinogram of the left eye	NR
Dehmel & Banbrink [13]	1971	1	8	m	strabismus convergens	NR
Taysi et al. [64]	1971	1	1	m	normal motor and mental development, normal hearing	NR

Table 3 continued

Author	Year	Cases	Age	Sex	Neurological symptoms	central nervous system radiographs
Kadrnka-Lovrenic et al. [33]	1973	2	0 NR	f f	psychomotor retardation, nystagmus NR	Xray of the skull was normal NR
Dudgeon & Chisholm [14]	1974	1	19 46 14 13 22 NR	f f m m m 2f	glaucoma and myopia, visual loss NR decreased visual acuity NR NR one of them blind	NR
Gellis & Feingold [21]	1974	1	NR	f	NR	NR
Guizar-Vázquez et al. [28]	1975	4	NR 24 0 60	f f m f	squinting slightly decreased visual acuity died after 23 days NR	persisting cranial suture on skull Xray NR NR NR
Haines & Rogers [30]	1975	1	20	m	decreased visual acuity on the right	
Zach [73]	1975	5	10 11 4 NR NR	f m f f m	verbal IQ 84, performance IQ 86, normal hearing strabismus NR NR NR	NR lack of frontal sinus development NR Xray of the skull showed thick calvarium and sclerotic mastoids NR
Weintraub et al. [69]	1975	3	f m m	21 28 56	esotropia, poor vision on the left, normal intelligence, muscle tone and reflexes were normal poor vision NR	Xray of the skull was normal
Vittori & Carbonnel [68]	1976	1	f	19	NR	Xray of the skull showed dolichocephaly
Gemme et al. [22]	1976	1	m	2	anophthalmia, normal EEG and CSF	Xray of the skull revealed macrocrania
Weintraub et al. [70]	1976	2	f m	20 28	NR NR	Xray of the skull revealed a deviated nasal septum; frontal, maxillary, sphenoid, and ethmoidal sinuses were present and within normal limits NR
Fara et al. [16]	1977	6	f m m f f m	30 10 6 21 5 1	NR reduced visual acuity, strabismus reduced visual acuity, strabismus NR NR strabismus	NR NR
Schneider et al. [55]	1977	1	m	11	bilateral ptosis, normal mental development, horizontal nystagmus, reduced visual acuity, squinting, bilateral conductive hearing loss	NR
Thoden et al. [65]	1977	4	4 3 28 2	f f m m	normal intelligence normal intelligence normal intelligence nystagmus, conductive hearing loss, subnormal intelligence	normal skull Xray NR NR slight central atrophy on pneumencephalography
Farman et al. [17]	1977	1	22	m	history of encephalitis age 4, progressive ataxia since age 6, reduced visual acuity, spastic diplegia, normal EEG	ventricles on the upper limit of normal size on the air encephalography, no evidence of cortical degeneration
Woolridge et al. [72]	1977	6	NR	4f 2m	NR	NR
Cox et al. [11]	1978	4	NR	NR	hyperactive deep tendon reflexes, ataxia, dysarthria and tibial muscle weakness in all 4, the oldest affected individual was wheelchairbound	NR
Levai et al. [35]	1979	2	NR	m m	normal intelligence, abnormal audiogramme normal intelligence, normal audiogramme	NR

Table 3 *continued*

Author	Year	Cases	Age	Sex	Neurological symptoms	central nervous system radiographs
Judisch et al. [32]	1979	4	NR	f	bilateral conductive hearing loss, increase in disc vessels	NR
			14	m	increase in disc vessels	
			13	f	hyperactivity (treated with dextroamphetamine),	
			7	f	esotropia	
Opijordsmoen & Nyberg-Hansen [48]	1980	9	46	m	supranuclear neurogenic bladder paresis, spasticity, bilateral sensorineural hearing loss, decreased visual acuity, EEG normal, CSF: elevated protein	spinal cord was normal on myelography
			62	m	spastic paraplegia, bladder disturbance	NR
			56	m	spastic paraplegia, bladder disturbance	
			55	m	spastic paraplegia, bladder disturbance	
			48	f	spastic paraplegia, bladder disturbance	
			41	m	spastic paraplegia, bladder disturbance	
			26	m	spastic paraplegia, bladder disturbance	
			14	f	spastic paraplegia, bladder disturbance	
			7	m	spastic paraplegia, bladder disturbance, epilepsy	
Audry et al. [1]	1981	1	36	m	spastic tetraparesis, bladder disturbance, paraesthesias in both legs, normal nerve conduction studies, EMG, EEG	normal densitometric tomography of the cerebral structures
Barnard et al. [2]	1981	2	28	m	blind since age 6, gaze palsy, nystagmus, progressive gait disturbance since childhood due to spasticity, blind, nystagmus on lateral gaze, progressive gait, normal intelligence	bilateral dense calcification of the basal ganglia in CT, narrowing of the spinal canal
			24	m	disturbance since age 18 (spasticity)	calcification of the basal ganglia on CT, mild hydrocephalus, spinal cord atrophy on myelography
Nivelon-Chevallier et al. [44]	1981	1	36	m	trouble walking, normal visual acuity, normal muscle tone, normal intelligence, spastic paraplegia, bladder disturbance, EEG and nerve conduction studies were normal	tomodensitometry of the cerebral structures was normal, slight deviation of C2-vertebra, normal myelography
			52	m	trouble walking most likely due to spasticity	
Novotny & Sterbova [46]	1984	42	NR	28m 14f	4 with glaucoma, 7 with strabismus 6 with glaucoma, 4 with strabismus	NR
Patton & Laurence [49]	1985	3	6	f	conductive hearing loss, strabismus	NR
			15	f	normal psychomotor development	
			43	m	NR	
Dean et al. [12]	1986	6	2	m	NR	dental films
			NR	4f		
				m		
Levine [36]	1986	1	25	f	Nystagmus, deterioration of vision, glaucoma	NR
Schuller et al. [53]	1986	1	35	m	mentally retarded	NR
Camera et al. (syndactyly and facial abnormalities) [9]	1994	2	NR	m	NR	NR
			NR	m	NR	NR
Grubs et al. [27]	1994	2	39	f	progressive paresthesia and muscle weakness	MRI changes including the globus pallidus, substantia nigra, red nucleus and cortex bilaterally in both, mild spinal cord atrophy in both
			15	f	no neurological dysfunction	
Norton et al. [45]	1995	6	41	m	spasticity of lower limbs with hyperreflexia, no evidence of hearing loss	MRI demonstrated white matter changes with areas of high signal intensity
			19	m	migraine, conductive hearing loss	no MRI scans per the family's wishes
			15	m	mild conductive hearing loss	
			12	m	mild hearing loss, history of fecal incontinence, pain in the lower limbs	
			11	m	cognitively "slow"	
			2	f	unremarkable	

Table 3 continued

Author	Year	Cases	Age	Sex	Neurological symptoms	central nervous system radiographs
Braun et al. [7]	1996	1	8	m	glaucoma	NR
Schrander-Stumpel & Franke [57]	1996	1	60	f	Trouble walking and bladder disturbance since the age of 40, spasticity, bilateral Babinski sign, heavy headache attacks and visual disturbances	MRI changes including small zones with low signal intensity in the globus pallidus, no white matter abnormalities
Ginsberg et al. [24]	1996	2	39	f	abnormal gait, upper and lower limb weakness, increased deep tendon reflexes, upgoing toes, progressive paraesthesiae, decreased proprioception below the knees, loss of bladder and bowel control	cerebral atrophy on CT MRI showed abnormal high white matter signal, low signal in the globus pallidus, substantia nigra, red nuclei and the parietooccipital cortex bilaterally, moderate spinal cord atrophy on MRI
Ioan et al. [31]	1997	3	15	m	normal neurologic examination	similar MRI-findings
			5	f	normal intelligence, no behavioural problems	
Shapiro et al. [59]	1997	8	4	m	mildly retarded psychomotor development	increased signal on T2-weighted images bilaterally in the periventricular region, particularly in the parieto-occipital regions, on MRI, thickened calvaria on Xray
			61	f	unremarkable	
			50	m	unremarkable	
			51	m	spastic bladder, spastic & atactic gait, tremor	
			49	m	unremarkable	
45	f	spastic bladder, spastic/atactic gait, tremor				
42	f	spastic bladder, spastic/atactic gait, oculomotor square wave jerks, normal CSF, normal EMG and nerve conduction studies				
Thomsen et al. [66]	1998	4	11	f	spastic bladder, hyperreflexia	occipital subcortical white matter changes on MRI
			16	m	spastic bladder, spastic/atactic gait	
			40	f	NR	
			NR	f	NR	
Stanislaw et al. [61]	1998	9	4	f	conductive hearing loss	MRI changes in the subcortical white matter of the right temporal lobe, normal CT
			6	f	excitement caused vomiting	
			19	f	seizures, decreased visual acuity, EEG showed mild occipital slowing bilaterally	
Ferencz & Salacz [19]	2000	1	0	f	NR	NR
			NR	m	NR	
			2f		one with glaucoma	
			4m		NR	
Ferencz & Salacz [19]	2000	1	10	m	Decreased visual acuity, Mental retardation	NR

CSF cerebrospinal fluid, CT computertomography, EEG electroencephalography, EMG electromyography, ERG electroretinogramme, f female(s), IQ intelligence quotient, NR not reported, m male(s), MRI magnetic resonance imaging, ODDD oculodentodigital dysplasia

al. specifically suggested the myristolated alanine-rich C kinase substrate (MARCKS) gene as a possible candidate. A GCT tripnucleotide repeat within this gene supports this hypothesis [5]. Furthermore a deficiency of the gene product was shown to produce abnormal cerebral development in mice [62]. The broad spectrum of clinical manifestations in ODDD with neurological, morphological, dental and ophthalmological symptoms may therefore be related to a trinucleotide mutation located on chromosome 6q22–23, possibly in the MARCKS gene. Further genetic studies and postmortem data may help to define the defect responsible for ODDD in the future.

Our index case is the first reported patient with ODDD

presenting with a hemisensory loss and therefore broadens the clinical spectrum of ODDD manifestations. Furthermore, muscle responses upon electromagnetic transcranial stimulation of the motor cortex prove involvement of the central part of the motor pathway, as spinal responses to magnetic stimulation were normal. Corresponding to our and to previous MRI findings, neuropsychological testing showed visuospatial deficits, indicating involvement of the occipitoparietal cortex.

Conclusion

Oculodentodigital dysplasia is associated with a broad spectrum of neurological symptoms. The finding of abnormal CNS white matter by MRI evaluation may explain some neurological symptoms, including the lower limb spasticity in our patients as well as in previously

described cases. Therefore, we conclude that leukocephalopathy associated with neuromanifestations is a presentation of ODDD in some cases. We recommend a complete neurological examination and an MRI of the brain in all patients with clinical symptoms suggestive of ODDD.

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