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*Clinical Report*

# DOOR Syndrome: Clinical Report, Literature Review and Discussion of Natural History

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DOOR syndrome (deafness, onychodystrophy, osteodystrophy, and mental retardation) is a rarely described disorder with less than 35 reports in the literature. The hallmarks of the syndrome, represented in the DOOR acronym, include sensorineural hearing loss, hypoplastic or absent nails on the hands and feet, small or absent distal phalanges of the hands and feet, and mental retardation. The purpose of our communication is to report on an additional patient with DOOR syndrome, delineate common as well as less frequent manifestations of DOOR syndrome, bring attention to the under appreciated facial features in DOOR syndrome, document the natural history of this disorder, and propose a suggested workup of those suspected of DOOR syndrome. DOOR syndrome is associated with characteristic, coarse facial features with large nose with wide nasal bridge, bulbous tip and anteverted nares, a long prominent philtrum and downturned corners of the mouth. The natural history is one of a deteriorative course, with progressive neurological manifestations including sensorineural deafness, seizures from infancy, optic atrophy, and a peripheral polyneuropathy. The majority of patients with DOOR syndrome have elevated levels of 2-oxoglutarate in the urine and plasma. In this report, we present a newborn with manifestations consistent with DOOR syndrome and a progressive clinical course. A comprehensive literature review reveals 32 patients with DOOR syndrome. In conclusion, DOOR syndrome is a neurometabolic disorder with recognizable facial features and a progressive natural history. © 2007 Wiley-Liss, Inc.

**Key words:** DOOR syndrome; onychodystrophy; osteodystrophy; sensorineural deafness; mental retardation; 2-oxoglutarate; metabolic syndrome

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## INTRODUCTION

DOOR syndrome (deafness, onychodystrophy, osteodystrophy, and mental retardation) is a rarely described disorder with less than 35 clinical reports in the literature. The hallmarks of the syndrome, represented in the DOOR acronym, include sensorineural hearing loss, small or absent nails on the hands and feet, small or absent distal phalanges of the hands and feet, and mental retardation. DOOR syndrome is associated with characteristic, coarse facial features, neurological manifestations including seizures from infancy, optic atrophy, and a peripheral polyneuropathy, as well as occasional dental, cardiac, and renal anomalies. Inheritance is presumably autosomal recessive. Genetic heterogeneity, especially within the early case reports of DOOR syndrome, has been suggested [Sanchez et al., 1981; Nevin et al., 1982]. The DOOR acronym was formalized in 1974 in a case report of a woman with profound mental retardation, sensorineural deafness, and anomalies of the digits and nails [Cantwell, 1975]. The majority of patients with DOOR syndrome have elevated levels of 2-oxoglutaric acid in the urine and plasma [Patton et al., 1987]; however this is not a consistent finding among all reports [Lin et al., 1993; Bos et al., 1994; Felix et al., 2002]. Those with DOOR syndrome were found in a case-control study to have decreased activity of the E1 component

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of the 2-oxoglutarate dehydrogenase complex, a finding that has not yet been repeated [Surendran et al., 2002]. However, the gene *OGDH*, which encodes the E1 component of the 2-oxoglutarate dehydrogenase, has been recently excluded as the underlying genetic defect in DOOR syndrome [Van Bever et al., 2007]. Thus, the etiology of DOOR syndrome remains unknown. In this report, we present a female infant born with physical findings consistent with DOOR syndrome, elevated urinary 2-oxoglutarate, and a progressive clinical course. A literature review, delineation of the DOOR phenotype including facial features, and summary of the natural history will follow.

## CLINICAL REPORT

The patient was born at 34 and 3/7 weeks gestation to a 20-year-old gravida 1 para 0–1, African-American mother. Prenatal history was significant for polyhydramnios and an abnormal 1 hr glucose challenge test with a normal 3 hr glucose tolerance test. All other prenatal labs were normal and the pregnancy was uncomplicated by infection or teratogen exposure.

The infant was delivered via normal spontaneous vaginal delivery. Birth weight was 2,915 g (90th centile), head circumference of 34 cm (90th centile), and length of 45 cm (40th centile). A three-vessel cord with very large umbilical vein, edematous placenta, and multiple cysts on the placental surface, 1–2 cm in diameter, were noted on delivery. The infant had mild respiratory distress, and was admitted to the neonatal intensive care unit. At this time, she was found to have multiple congenital anomalies and a genetics consultation was obtained.

Initial physical exam revealed coarse facial features with a high forehead, large anterior fontanelle, shallow supraorbital ridges, and redundancy of tissue at the glabellar area (Fig. 1.1). Mild hypertelorism, bilateral epicanthal folds and lower canthal folds were noted. Nose was high set with a broad bridge, broad mid nose, prominent nasal tip, and large nares. Philtrum was long and prominent. Mouth was large with well-formed upper lip, thick and slightly everted lower lip, and down turned corners of the mouth. Additional findings include, hyperplastic, thick palatine ridges (Fig. 1.3), a V-shaped cleft of the posterior palate, a bifid uvula, prominent cheeks, slightly small mandible, deep submental groove, posteriorly rotated ears with prominent, over-folded helices and anti-helices (Fig. 1.2), and nuchal thickening. Genital examination showed normal female. Extremities were remarkable for abnormal fingers and toes. Anomalies of the digits include abnormal thumbs which were proximally placed, radially deviated and with a broad distal phalanx (Fig. 1.4), short index fingers, hypoplastic distal phalanges of the second

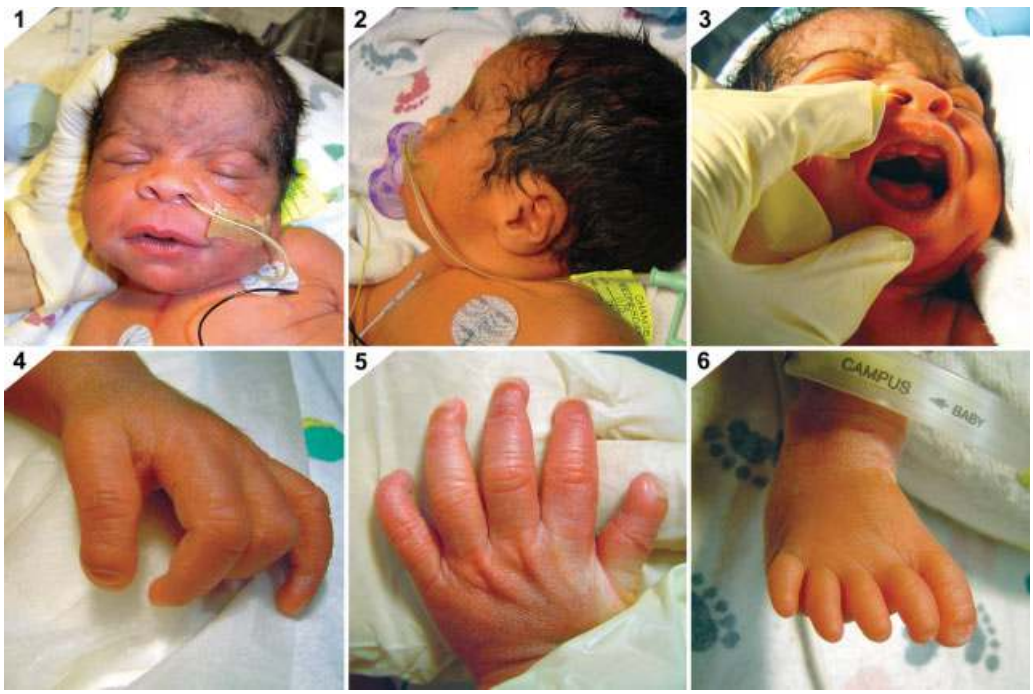


FIG. 1. (**1**) Coarse facial features at birth, hypertrichosis of forehead and brows, epicanthal and lower canthal folds, wide nasal bridge, large anteverted nares, prominent smooth philtrum, full lower lip and full cheeks, (**2**) Posteriorly rotated ears with overfolded helixes, (**3**) Hyperplastic, thick palatine ridges, (**4**) Abrupt tapering of digits II through V with hypoplastic terminal phalanges, clinodactylous digit V, small and deep-set nails throughout, (**5**) Long thumbs bilaterally with broad terminal phalange, (**6**) Hypoplastic toenails throughout, with nails nearly absent on digits IV and V, short digits III through V. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

through fifth digits bilaterally, bilateral fifth finger clinodactyly and small, deep-set nails throughout (Fig. 1.5). Anomalies of the toes include brachydactyly of third, fourth and fifth toes, hypoplastic nails of the 1st through 4th digits and nearly absent nail of the 5th digits bilaterally (Fig. 1.6). The infant has significant hypertrichosis of her scalp hair as well as her forehead, eyebrows and upper shoulders. Neurological examination was remarkable for hypotonia, hyporeflexia, and a poor suck reflex.

Cytogenetic analysis revealed a normal 46,XX karyotype. Hearing tests documented profound bilateral sensorineural deafness. Full skeletal radiographs were significant for distal limb abnormalities (Fig. 2). X-rays of both hands showed distal phalangeal hypoplasia involving the first through fifth digits bilaterally. X-rays of both feet revealed bilateral hypoplasia and faint ossification of the distal phalanx of the great toes. The second, third, and fourth toes contained only two phalanges. The distal phalanges of the fifth toes were hypoplastic. Brain MRI showed mild prominence of the sulci, ventricles, and basilar cisterns with simplified gyral patterns, pontine and cerebellar hypoplasia, and delayed myelination. The patient was found to have an elevated urinary 2-oxoglutaric acid in urine, 1,374 mmol/mol creat (nl <110). Other urinary organic acids measured over two times the upper limit of normal include lactic acid (352 mmol/mol creat), malic acid (110 mmol/mol creat) and 2-hydroxyglutaric acid (62 mmol/mol creat), citric acid (998 mmol/mol creat), and 4-hydroxyphenylpyruvic acid (12 mmol/mol creat). The infant had normal ophthalmologic exam, echocardiogram, electroencephalogram (EEG), head ultrasound, and abdominal ultrasound, with an incidental 6 mm interpolar renal cyst. Activity of the 2-ketoglutarate dehydrogenase complex (KDC) was assessed as previously described [Sheu et al., 1981; Chuang et al., 1983; Kerr et al., 1987]. The activity of the KDC was found to be normal (2.30 nmol/min/mg protein; control mean 2.07, standard deviation 0.92).

Her clinical course was notable for feeding intolerance and a very ineffective suck demonstrated by modified barium swallow, requiring nasogastric feeds. In the second week of life and in the setting of feeding intolerance, abdominal X-ray strongly suggested malrotation of the midgut with volvulus or GI obstruction. The infant underwent an exploratory laparotomy but no abnormality was noted. Severe gastroesophageal reflux was diagnosed by pH probe and treated with an H2 receptor blocker. Feeding was started by gastrostomy tube, and subsequently the infant developed aspiration pneumonia. Throughout the first month of life, waxing and waning jitteriness of the extremities was noted and questioned as seizure activity. Multiple antiepileptic medications, including valproic acid and klonopin have not had therapeutic benefit. At 7 months of age, the patient had been admitted to the hospital on five occasions for respiratory infections. Re-examination revealed increased coarsening of the facial features (Fig. 3). At 10 months of age, the infant was found by the parents to be not breathing and unresponsive. CPR at the local hospital was attempted but unsuccessful.

Family history is negative for any individuals with deafness, nail dysplasia, congenital heart defects, cleft palate, or mental retardation. There was no known parental consanguinity.

## METHODS

An extensive literature review was conducted for DOOR syndrome. Applicable papers were compiled, excluding those without English translation [Thomas and Nevin, 1982; Szabo et al., 2004]. In reviewing these cases, we recognized that they appeared to represent a heterogeneous group of disorders. In order to optimize the homogeneity of our literature review, exclusion criteria were chosen including (1) both parent and child with clinical features of DOOR syndrome, and (2) absence of both mental retardation and seizures. Six patients from three case reports were excluded [Feinmesser and Zelig, 1961; Goodman et al., 1969; Moghadam and Statten, 1972]. The patients described by Feinmesser and Zelig have only deafness and onychodystrophy, without mental retardation, seizures or radiographic findings consistent with DOOR syndrome. The patients

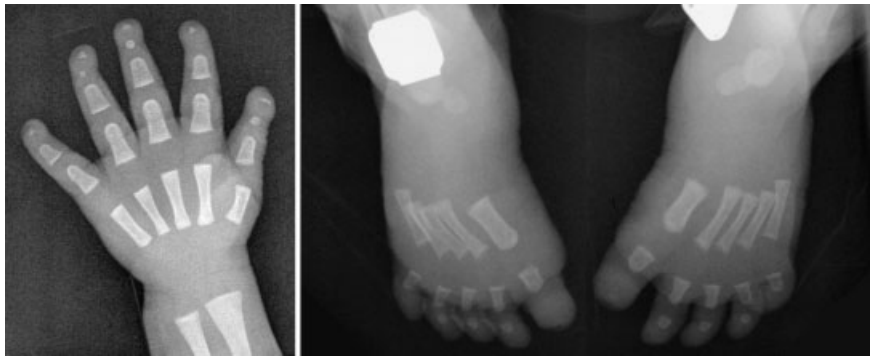

Fig. 2. Left hand and feet X rays at 5 days of life, demonstrating distal phalangeal a/hypoplasia.

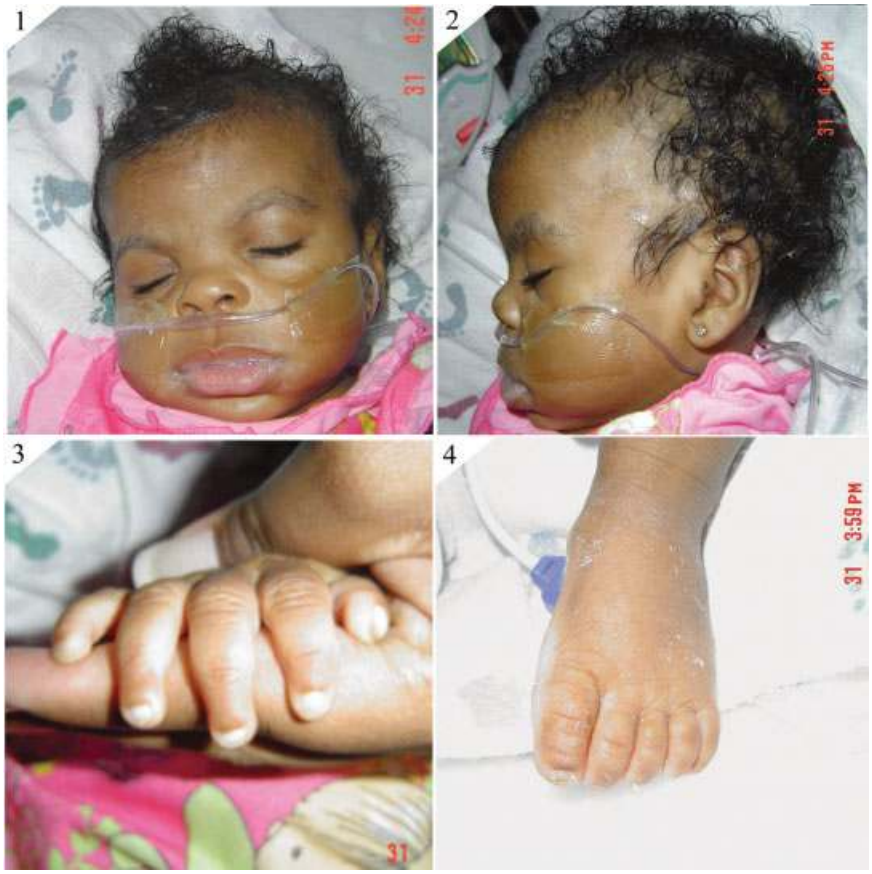


FIG. 3. (1) At 7 months of age, patient shows noticeable coarsening of the facial features. (2) Profile of patient with large ears and thick lower lip held in an open position. (3) Tapering of the distal phalanges. (4) Toenail a/hypoplasia again observed. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

described by Goodman et al. as well as by Moghadam and Statten are mother/son pairs with onycho-osteodystrophy and deafness, but without retardation, seizures, or the characteristic facial features of DOOR syndrome. These last cases may represent a separate autosomal dominant, pseudo-dominant or X-linked condition, (Goodman–Moghadam syndrome), and will not be discussed further. So as to better characterize the facial features of DOOR syndrome, those case reports with accompanying photographs were independently reviewed by two of our co-authors (M Golabi and B Hall).

## RESULTS

Tables I–III represent the physical findings of 32 patients with DOOR syndrome compiled from 18 publications. A discussion of the manifestations and natural history of DOOR syndrome will follow.

### Phenotypic Features

Profound, bilateral sensorineural deafness as documented by brain stem auditory evoked responses (BAER) is nearly universal in DOOR syndrome. Initial case reports considered sensorineural deafness to be congenital [Cantwell, 1975], and indeed hearing tests soon after birth have revealed profound sensorineural deafness [Patton et al., 1987; Thornton et al., 1994; Van Bever et al., 2007]. However, variability exists in the presentation of hearing loss. A case report of DOOR syndrome with mild unilateral deafness at birth was recently published [Van Bever et al., 2007]. Two reports with DOOR syndrome have been documented to have a gradual, progressive deafness. These include one report with progressive hearing loss until profound deafness at age four [Sanchez et al., 1981], as well as a case with mild unilateral hearing loss progressing to profound bilateral hearing loss [Hess and Pecotte, 1984]. It may well be that a progressive sensorineural hearing loss has been missed in the many cases in which formal hearing tests were delayed.

Characteristic malformations of the nails and digits (onycho-osteodystrophy) are universal features of DOOR syndrome. Examination of the hands reveals small or absent nails in all cases. Fingernails I and/or V are often absent, while others are hypoplastic [Walbaum et al., 1970; Sanchez et al., 1981; Lin et al., 1993; Felix et al., 2002]. The thumb may be

TABLE I. Major Clinical Manifestations and Demographics

| | Qazi | Walbaum (A) | Walbaum (B) | Cantwell | Sanchez (A) | Sanchez (B) | Nevin (A) | Nevin (B) | Qazi (A) | Qazi (B) | Hess | Eronen (A) | Eronen (B) | Eronen (C) | Patton (A) | Patton (B) | Patton (C) | Le Merrer (A) | Le Merrer (B) | Bos | Lin | Thornton (A) | Thornton (B) | Reardon | Rajab[a] | Felix (A) | Felix (B) | Felix (C) | van Bever (A) | van Bever (B) | James | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Demographics | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Age | 5 | 13 | 3 | 14 | 16 | 14 | 2 | 11 | 10 | 9 | 11 | 1 | 2 | 0 | 5 | NR | NR | 0 | 1 | 5 | 11 | 0 | 0 | 0 | 1 | 3 | 3 | 2 | 2 | 1 | 0 | |
| Sex | M | F | M | F | F | F | M | M | M | F | F | M | F | F | F | M | F | M | F | M | F | F | F | F | F | M | F | F | F | M | F | |
| Ethnicity/country of origin | Puerto Rican | France | France | Latina | Venezuela | Venezuela | Irish | Irish | Puerto Rican | Puerto Rican | N. European | Finland | Finland | Finland | Italian | Pakistani | Pakistani | France | France | Brazilian | Guatemalan | Ireland | Ireland | Britain | Omani | Brazilian | Brazilian | Brazilian | Moroccan | Moroccan | African American | |
| Family history | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Consanguinity | − | − | − | + | + | + | + | − | − | − | − | − | + | + | − | + | + | − | − | − | − | − | − | − | + | − | − | − | − | − | − | 29% (9/31) |
| Affected siblings | − | + | + | − | + | + | − | − | + | + | − | − | + | + | − | − | − | − | − | − | − | + | + | − | + | − | − | − | + | + | − | 39% (12/31) |
| Major clinical manifestations | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Craniofacial | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Narrow bifrontal diameter | NR | NR | NR | NR | + | + | NR | + | − | + | NR | − | NR | NR | + | + | + | + | − | + | NR | NR | NR | NR | NR | + | − | NR | + | − | + | 71% (12/17) |
| Coarse facies | + | NR | NR | NR | + | + | NR | − | + | + | NR | + | NR | NR | + | + | + | + | + | − | NR | NR | NR | NR | NR | − | − | NR | + | + | + | 78% (14/18) |
| Broad nasal bridge | NR | NR | NR | NR | + | + | NR | + | + | + | NR | + | + | + | NR | + | NR | NR | + | + | + | + | + | − | NR | + | + | NR | + | + | + | 95% (18/19) |
| Bulbous nasal tip | + | + | NR | NR | + | + | NR | + | + | + | NR | + | NR | NR | + | + | + | + | + | + | NR | + | + | NR | NR | + | + | NR | + | NR | + | 100% (20/20) |
| Large/ anteverted nares | + | NR | + | NR | + | + | NR | − | + | + | NR | + | NR | NR | + | + | + | + | + | + | NR | + | + | NR | NR | − | + | NR | + | NR | + | 90% (18/20) |
| Long/prominent philtrum | + | NR | + | NR | + | + | NR | + | + | + | NR | + | NR | NR | + | + | + | + | + | + | NR | + | + | NR | NR | − | + | NR | + | NR | + | 95% (19/20) |
| Open mouth | NR | NR | NR | NR | − | − | NR | + | + | + | NR | + | NR | NR | + | + | − | + | + | − | NR | NR | NR | NR | NR | − | + | NR | + | + | + | 71% (12/17) |
| Downturned cornors of mouth | + | NR | NR | NR | + | − | NR | + | + | + | NR | − | NR | NR | + | + | + | + | + | − | NR | NR | NR | NR | NR | + | + | NR | + | + | + | 83% (15/18) |
| Thin upper lip | − | NR | NR | NR | − | − | NR | − | + | − | NR | + | NR | NR | + | + | + | + | + | + | NR | + | − | + | NR | + | + | NR | − | + | − | 62% (13/21) |
| Full lower lip | + | NR | NR | NR | + | + | NR | + | + | + | NR | + | NR | NR | − | + | + | − | − | + | NR | NR | NR | + | NR | − | − | NR | + | + | + | 74% (14/19) |
| Low set ears | + | NR | NR | NR | NR | NR | NR | NR | NR | + | NR | + | + | + | NR | − | − | + | + | − | NR | − | + | NR | NR | − | − | − | NR | + | + | 59% (10/17) |
| Limb | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Long fingerlike thumb(s) | + | + | + | + | + | + | + | + | + | + | − | − | NR | NR | − | − | − | − | − | − | + | + | + | − | − | + | + | − | NR | + | + | 61% (17/28) |
| Digit V brachdactyly | + | + | + | + | + | + | + | + | + | + | − | − | NR | NR | + | + | − | − | − | + | + | + | − | + | − | + | + | + | + | + | − | 72% (21/29) |
| Fingernail a/ hypoplasia | + | + | + | + | + | + | + | + | + | + | NR | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 100% (30/30) |
| Toenail a/hypoplasia | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 100% (31/31) |
| Neurologic | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Sensorinerual deafness | + | + | + | + | + | + | + | + | + | + | + | + | NR | NR | + | + | + | NR | + | + | + | + | NR | + | + | + | + | + | + | + | + | 100% (27/27) |
| Optic atrophy | − | − | − | − | − | − | + | − | − | − | + | + | NR | NR | + | + | − | + | + | − | − | − | − | NR | + | − | − | − | − | − | − | 29% (8/28) |
| Developmental delay | NR[b] | + | + | + | + | + | + | + | + | + | + | + | + | NR | + | + | + | NR | + | + | + | NR | NR | NR | + | + | + | + | + | + | NR | 100% (24/24) |
| Convulsions | + | + | − | + | + | + | + | − | + | + | + | + | + | − | + | + | + | + | − | + | + | + | + | + | + | + | + | +[c] | + | + | + | 87% (27/31) |

[a]Cases 2–4 excluded for lack for lack of information.
[b]Patient not formally tested.
[c]Information obtained from personal communication.

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TABLE II. Less Frequent Manifestations and Diagnostic Studies

| | Qazi | Walbaum (A) | Walbaum (B) | Cantwell | Sanchez (A) | Sanchez (B) | Nevin (A) | Nevin (B) | Qazi (A) | Qazi (B) | Hess | Eronen (A) | Eronen (B) | Eronen (C) | Patton (A) | Patton (B) | Patton (C) | Le Merrer (A) | Le Merrer (B) | Bos | Lin | Thornton (A) | Thornton (B) | Reardon | Rajab | Felix (A) | Felix (B) | Felix (C) | van Bever (A) | van Bever (B) | James | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Less frequent clinical manifestations | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Craniofacial | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Microcephaly | − | − | NR | − | − | − | − | − | − | − | − | + | + | + | + | − | − | − | + | − | − | NR | NR | − | + | + | − | − | − | NR | | 27% (7/26) |
| Low frontal hairline | NR | NR | NR | NR | − | + | + | − | − | − | NR | − | NR | NR | − | + | + | NR | NR | − | NR | NR | NR | NR | NR | + | − | NR | − | − | + | 33% (5/15) |
| Hypertelorism/ laterally displaced inner canthi | NR | NR | NR | NR | − | − | + | + | + | + | NR | − | NR | NR | − | − | + | − | − | − | NR | − | + | NR | NR | − | + | NR | − | + | + | 53% (8/15) |
| Epicanthal/lower canthal folds | + | NR | NR | NR | − | − | + | − | − | − | + | − | NR | NR | + | − | + | − | − | − | NR | NR | NR | NR | NR | − | + | NR | + | + | + | 42% (8/19) |
| Ptosis | NR | NR | NR | NR | − | + | + | − | + | − | NR | − | NR | NR | + | − | − | − | − | + | NR | NR | NR | NR | NR | − | − | NR | − | − | − | 25% (4/16) |
| Hypertrophic gums | + | NR | NR | NR | NR | NR | + | NR | NR | NR | NR | + | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | + | 100% (3/3) |
| Dental anomalies | + | − | − | + | − | − | − | − | + | − | + | − | NR | NR | − | − | − | NR | NR | − | NR | NR | NR | NR | NR | − | − | NR | NR | NR | NR | 24% (4/18) |
| High arched palate | NR | NR | NR | NR | NR | NR | NR | NR | + | + | + | + | NR | NR | NR | NR | NR | + | NR | + | NR | NR | NR | NR | NR | − | − | NR | + | NR | − | 35% (7/20) |
| Cleft palate/ Submucous cleft palate | − | − | − | − | − | − | NR | − | − | − | + | − | NR | NR | − | − | − | − | − | − | NR | + | − | NR | NR | − | + | NR | − | − | + | 17% (4/24) |
| Nuchal thickening (pre- and postnatal) | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | − | + | NR | NR | − | + | NR | NR | NR | NR | NR | NR | NR | + | 60% (3/5) |
| Limb | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Digit II brachydactyly | − | − | − | − | − | − | + | − | + | + | − | − | NR | NR | + | + | − | − | − | + | − | − | − | − | − | + | + | − | − | − | + | 31% (9/29) |
| Digit V clinodactyly | + | + | + | + | − | − | + | + | + | + | − | − | NR | NR | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | + | 31% (9/29) |
| Large/squat great toe | + | NR | NR | − | NR | NR | + | + | + | − | − | − | NR | NR | + | − | − | − | − | − | + | − | − | NR | − | + | − | − | NR | NR | − | 33% (7/21) |
| Other | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Congenital heart disease | − | − | − | − | − | − | − | − | − | − | − | − | NR | PDA/PFO | − | − | − | − | − | − | − | ASD/VSD | ASD/VSD | − | − | VSD | − | − | − | PDA | − | 17% (5/30) |
| Urinary tract abnormalities | − | − | − | − | − | − | − | − | − | − | − | + | NR | + | − | − | − | + | − | − | − | + | + | − | − | − | − | − | − | − | − | 17% (5/30) |
| Peripheral neuropathy | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | + | NR | NR | NR | NR | + | + | − | 100% (3/3) |
| Diagnostic studies | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hand X-ray: distal phalange a/ hypoplasia | + | + | + | + | + | + | + | + | + | + | + | + | + | NR | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 100% (30/30) |
| Hand X-ray: triphalangeal thumb | + | + | + | + | + | + | − | − | + | − | − | − | NR | NR | − | − | + | − | − | − | − | − | − | − | − | − | − | − | + | − | − | 31% (9/29) |
| Foot X-ray: distal phalange a/hypoplasia | NR | + | + | + | + | + | + | + | + | + | + | + | + | NR | + | + | + | + | + | + | + | + | + | NR | + | + | + | + | + | + | + | 100% (29/29) |
| Abnormal brain imaging (CT and MRI) | NR | NR | NR | NR | NR | NR | − | NR | NR | NR | NR | + | NR | + | = | − | − | NR | + | NR | − | + | NR | NR | + | + | + | NR | + | + | + | 67% (10/15) |
| Abnormal EEG | NR | NR | NR | + | + | + | + | NR | NR | NR | + | + | NR | NR | NR | + | + | + | NR | NR | − | + | NR | + | + | NR | − | NR | + | + | − | 82% (14/17) |
| Elevated plasma 2-oxoglutarate | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | + | + | + | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | − | − | NR | 60% (3/5) |
| Elevated urine 2-oxoglutarate | NR | NR | NR | NR | NR | NR | NR | NR | + | NR | NR | NR | NR | NR | + | + | + | NR | NR | − | − | NR | NR | + | + | − | − | − | + | + | + | 64% (9/14) |
| Normal Karyotype | + | + | + | + | + | + | + | NR | + | + | + | + | NR | NR | + | + | NR | + | + | + | + | + | + | NR | + | + | + | + | + | NR | + | 100% (25/25) |

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TABLE III. Rare Features of DOOR Syndrome

| Craniofacial | Musculoskeletal | Neurologic | Other |
|---|---|---|---|
| Absent external auditory meatus | 12th rib aplasia | Arhinencephaly | Ambiguous genitalia |
| Cataracts | Equinovarus deformity | Dandy–Walker | Large, unusually shaped adrenal glands |
| Coronal synostosis | Hemivertebrae | Micropolygyria | Placental cysts |
| Nystagmus | Lumbar scoliosis | | Thrombocytosis |
| Strabismus | Partial cutaneous syndactyly | | |
| | Sirenomelia | | |
| | Spina bifida occulta | | |
| | Symphangalism | | |

long, "fingerlike" with an extra flexion crease and bulbous terminal phalange. Second and fifth finger brachydactyly as well as fifth finger clinodactyly are observed (see Tables I and II). Unilateral and/or bilateral triphalangeal thumbs are found in 31% (9/29) of case reports, the presence of which is unrelated to clinical severity [Lin et al., 1993]. The terminal phalanges of digits II–V are in all cases either hypoplastic or absent; most commonly the terminal phalanges of digits II and/or V are absent [Bos et al., 1994]. Symphalangism of the distal interphalangeal joint has been described [Cantwell, 1975; Nevin et al., 1982]. Examination of the feet reveals disproportionately large and long toes, 36% (8/22). A case of bilateral triphalangeal great toes has been described [Qazi and Smithwick, 1970]. Toenails are generally hypoplastic, however complete absence of all toenails is not uncommon [Nevin et al., 1982; Qazi and Nangia, 1984; Eronen et al., 1985]. Foot radiographs shows absence or hypoplasia of the terminal phalanx of digits II–V. Digit V may be more severely affected, with absence of the distal and middle phalanx or entire toe [Nevin et al., 1982; Eronen et al., 1985; Patton et al., 1987; Rajab et al., 2000; Felix et al., 2002].

Distinct facial features represent a major clinical finding in DOOR syndrome. These include a coarseness of the facial features, with narrow bifrontal diameter, broad nasal bridge with large, anteverted nares, long and prominent philtrum, long upper lip with thin vermilion border, fleshy everted lower lip and downturned corners of the mouth often held in an open position, high arched palate with thick palatine ridges and low-set ears. See Tables I and II for a comprehensive tabulation of facial features and their relative frequencies in DOOR syndrome. As illustrated in the tables, those infants that share the most resemblance to our case include the patient reported by Eronen and the third patient reported by Patton [Eronen et al., 1985; Patton et al., 1987].

Ophthalmologic anomalies are found in 43% (13/30) of DOOR patients. The most common ophthalmologic anomaly is optic atrophy leading to blindness, 29% (8/28). When tested, visual evoked potentials and flash electroretinogram have showed an impaired response of outer retinal receptors [Reardon et al., 1981; Sadoun et al., 1989; Van Bever et al., 2007]. High myopia, cataracts, iris hypoplasia, retinal detachment, nystagmus and strabismus are occasional findings [Hess and Pecotte, 1984; Patton et al., 1987; Felix et al., 2002; Van Bever et al., 2007].

Less common findings in DOOR syndrome include dental, cardiac, and renal abnormalities. Dental anomalies have been documented in 24% (4/18) of patients old enough for evaluation to be performed. Anomalies range from hypoplastic enamel and yellow discoloration [Cantwell, 1975; Qazi and Nangia, 1984] to more striking dental anomalies included wide spacing and abnormal size, shape and number of teeth [Qazi and Smithwick, 1970; Hess and Pecotte, 1984].

Congenital heart defects (CHD) have been documented in 16% (5/31) of patients with DOOR syndrome. Cardiac evaluation ranged widely from simple auscultation, to chest X-ray, EKG and echocardiogram. Anomalies include patent ductus arteriosus, as well as atrial and ventricular septal defects [Eronen et al., 1985; Thornton et al., 1994; Felix et al., 2002; Van Bever et al., 2007].

Genitourinary anomalies have been documented in 16% (5/31) of those with DOOR syndrome. They are quite variable and include unilateral renal agenesis, duplicated kidney, cystic dysplastic kidneys, and hydrouteronephrosis without obstruction [Eronen et al., 1985; Le Merrer et al., 1992; Thornton et al., 1994]. Two cases of urinary tract infections/urosepsis in the presence of urinary tract abnormalities have been reported [Eronen et al., 1985; Thornton et al., 1994]. Individuals with features of DOOR syndrome and renal malformations were once posited to have a separate syndrome (Eronen or digito-reno-cerebral syndrome) [Eronen et al., 1985; Le Merrer et al., 1992], however remarkable overlap in phenotype and elevated urine 2-oxoglutarate in a patient of Eronen et al. suggests that the Eronen and DOOR syndrome are identical [Winter, 1992; Thornton et al., 1994]. Thus, DOOR phenotype includes renal anomalies.

Neuroimaging studies often reveal abnormal findings in DOOR syndrome, 63% (10/16). Cerebral atrophy with or without dilated ventricles, and prominent sulci have been noted in a number of patients [Eronen et al., 1985; Le Merrer et al., 1992; Rajab et al., 2000; present

case report]. Varying degrees of defects in myelination have been observed, ranging from delayed myelination [Van Bever et al., 2007; present case] to "virtual absence of myelination" in a 5-month-old [Rajab et al., 2000]. Dandy–Walker malformation has been reported [Le Merrer et al., 1992], and in our case cerebellar and pontine hypoplasia was noted. Pathologic findings are rarely reported in the literature, however autopsy in one case revealed frontotemporal hypoplasia with arhinencephaly and polymicrogyria [Thornton et al., 1994]. Less frequent MRI findings include punctiform calcifications in the occipitotemporal region [Felix et al., 2002], hyperdensities in the pons cerebri and thin corpus callosum [Van Bever et al., 2007].

Other significant neurologic findings in DOOR syndrome include a/hyporeflexia in infants with DOOR syndrome [Reardon et al., 1981; Eronen et al., 1985; Patton et al., 1987; Le Merrer et al., 1992; Thornton et al., 1994; Van Bever et al., 2007]. This has been observed in the setting of a documented peripheral polyneuropathy in three patients [Reardon et al., 1981; Van Bever et al., 2007]. Reardon et al. evaluated a hyporeflexive infant by electromyogram (EMG) showing markedly reduced amplitude of muscle action potentials and nerve conduction studies found absent sensory potentials [Reardon et al., 1981]. Van Bever et al. reported two patients with arreflexia and abnormal EMGs suggestive of an axonal degenerative polyneuropathy [Van Bever et al., 2007]. EMG and nerve conduction studies have not been performed in the vast majority of DOOR patients with a/hyporeflexia, and with this consideration a high rate of undocumented peripheral neuropathy may be present in DOOR syndrome.

Elevated 2-oxoglutarate levels were first found in four patients with DOOR syndrome [Patton et al., 1987]. Nine patients have been shown subsequently to have elevated urinary 2-oxoglutarate [Reardon et al., 1981; Winter, 1992; Rajab et al., 2000; Surendran et al., 2002; Van Bever et al., 2007; present case report]. However, a single normal measurement of urinary 2-oxoglutarate has been described in a number of reports, and should not exclude the diagnosis of DOOR syndrome [Lin et al., 1993; Bos et al., 1994; Felix et al., 2002].

## Natural History

Clinical manifestations in the neonate and infant indicate a progressive clinical course. The key issues in the natural history of DOOR syndrome are neurodevelopmental features. The first neurologic manifestation of DOOR syndrome is in utero, with the common observation of polyhydramnios [Hess and Pecotte, 1984; Thornton et al., 1994; Van Bever et al., 2007; present case report]. In the newborn period, neurologic exam typically reveals a poor suck reflex, hypotonia, and a/hyporeflexia [Eronen et al., 1985; Patton et al., 1987; Le Merrer et al., 1992; Thornton et al., 1994; Van Bever et al., 2007]. Prolonged feeding difficulties are commonly observed in infants with DOOR syndrome, which may lead to growth retardation and necessitate tube feeds [Le Merrer et al., 1992; Reardon et al., 1981; Felix, personal communication; Van Bever et al., 2007]. In the setting of feeding problems, both severe gastroesophageal reflux and aspiration pneumonias have been reported [Felix, personal communication; Van Bever et al., 2007; present case report]. Respiratory distress in the neonatal period has been observed, of a central cause, and may be life threatening [Nevin et al., 1982; Eronen et al., 1985; Rajab et al., 2000; present case report]. Respiratory difficulties persist into infancy with apneic and/or cyanotic episodes, [Rajab et al., 2000; Felix, personal communication; Van Bever et al., 2007].

Seizure disorders from infancy are a prominent clinical manifestation, seen in 88% (28/32). Seizures in DOOR syndrome have a progressive nature, with increasing frequency and/or severity of seizures [Qazi and Nangia, 1984; Eronen et al., 1985; Patton et al., 1987; Rajab et al., 2000; Felix et al., 2002]. Those described are primarily generalized tonic clonic [Qazi and Smithwick, 1970; Cantwell, 1975; Qazi and Nangia, 1984; Patton et al. 1987; Sadoun et al., 1989; Felix et al., 2002], but myoclonic, partial, and suspected absence seizures have been individually reported [Rajab et al., 2000; Lin et al., 1993]. As in our case, myoclonus and/or tremors without gross seizures may be observed. The median age of onset of seizures is 6 weeks with a range from the first day of life to 8 years of age, however in the vast majority, 88% (23/26), seizures begin within the first year of life. Seizures on a daily basis are not unusual, episodes of status epilepticus are common [Qazi and Nangia, 1984; Eronen et al., 1985; Patton et al., 1987; Le Merrer et al., 1992], and for the most part seizures are poorly controlled with or refractory to multiple antiepileptic medications [Sanchez et al., 1981; Qazi and Nangia, 1984; Patton et al., 1987; Sadoun et al., 1989; Felix et al., 2002; Van Bever et al., 2007]. A report exists of seizures refractory to traditional antiepileptics responding to ACTH [Rajab et al., 2000]. Seizures are often precipitated by intercurrent infections [Qazi and Smithwick, 1970; Patton et al., 1987; Rajab et al., 2000]. Five deaths have been described in the setting of status epilepticus or after seizures [Eronen et al., 1985; Patton et al., 1987; Rajab et al., 2000; Felix et al., personal communication]. Descriptions of EEG findings vary, but commonly show high amplitude slow activity and spikes/sharp waves [Reardon et al., 1981].

From infancy a wide range of developmental delay exists among patients. Gross motor development is often delayed, 75% (12/16), but shows great variation in severity. Those least affected show mild delays in early motor milestones [Sanchez et al., 1981; Lin

et al., 1993]. On the other hand, those patients that are more severely affected may have persistent generalized hypotonia without achievement of any significant milestones [Hess and Pecotte, 1984; Patton et al., 1987; Van Bever et al., 2007]. There also exist documented individuals who clearly had a regression in motor milestones [Qazi and Nangia, 1984; Rajab et al., 2000]. In all case reports, language development is markedly delayed or absent. Logically this is due to a combination of cognitive difficulties compounded by profound hearing loss. Despite these difficulties, individuals on occasion have employed signing for expressive and receptive language [Cantwell, 1975; Lin et al., 1993]. Formal developmental or intelligence testing are available in six patients with this condition; 4/6 patients had developmental or intelligence quotients (IQ) indicating severe MR (<50) [Walbaum et al., 1970; Cantwell, 1975; Nevin et al., 1982; Qazi and Nangia, 1984], and the remaining had mild MR (50–70) [Qazi and Nangia, 1984; Lin et al., 1993].

Other neurodevelopmental manifestations deserve comment. Psychomotor agitation and/or unusual motor behavior distinct from seizure activity have been described. Descriptions include a moving of hands and head, occasional twisting and turning movements, or involuntary and sudden movements of all limbs [Qazi and Nangia, 1984; Bos et al., 1994; Lin et al., 1993; Van Bever et al., 2007]. These movement disorders may be constant or episodic in nature. Psychosocial adaptation for individuals with this condition may be challenging. In one case, episodes of inappropriate behavior including public removal of clothing and wandering have been described [Lin et al., 1993].

Thirty two percent (9/28) of those with DOOR syndrome have been documented to have early childhood mortality, before 2 years of age. The cause of death is most often status epilepticus [Eronen et al., 1985; Patton et al., 1987; Rajab et al., 2000]. Other causes include neonatal respiratory distress [Eronen et al., 1985], necrotizing enterocolitis related to prematurity, urosepsis related to urinary tract abnormalities [Thornton et al., 1994], and aspiration pneumonia related to feeding difficulties [Van Bever et al., 2007]. After 4 years of age, deaths have not been reported in DOOR syndrome, and thus after this point mortality curves may approximate those of the general population.

## DISCUSSION

We present a further case of DOOR syndrome. Characteristic coarse facial features as well as hand and nail malformations suggested the diagnosis on clinical grounds. Further studies were consistent with DOOR syndrome, including BAER which revealed profound bilateral sensorineural deafness, MRI which showed delayed myelination and cerebellar hypoplasia, and urine organic acids which revealed significantly elevated 2-oxoglutarate. The clinical course of our patient is similar to other severely affected infants, including neonatal hypotonia, feeding difficulties requiring tube feeds, increasing seizures, frequent aspiration pneumonias and respiratory infections, and poor neurodevelopment.

In our patient, re-evaluation showed increasingly severe manifestations of DOOR syndrome, particularly a noticeable coarsening of the facial features. A literature review confirms that indeed the natural history of this rare syndrome follows a progressive course. These manifestations include gradual deafness which has been found in a few patients, optic atrophy leading to blindness, a peripheral degenerative polyneuropathy discovered in three patients with DOOR syndrome, seizure disorders with increasing frequency and severity over time, and plateaued motor and intellectual development. We conclude that these progressive features of DOOR syndrome are consistent with a neurometabolic disorder. Further supporting a neurometabolic etiology, placental cysts found in our case and one previous case report support the understanding of this disorder as a metabolic syndrome [Rajab et al., 2000].

The differential diagnosis for DOOR syndrome includes Coffin-Siris syndrome, Zimmerman–Laband syndrome, fetal dilantin syndrome, and fetal alcohol syndrome. Coffin-Siris syndrome shares features with DOOR syndrome including a coarse facial appearance, and hypoplastic terminal phalanges and nails (particularly of the fifth digits and fourth and fifth toes) [Fleck et al., 2001]. Those with Coffin–Siris syndrome do not have deafness or optic nerve atrophy. Zimmerman–Laband syndrome shares features with DOOR syndrome including coarse facial features, gingival hyperplasia, hypoplastic distal phalanges, absent or dysplastic nails, and mental retardation (although unlike DOOR syndrome this is not a universal feature) [Laband et al., 1964; Van Buggenhout et al., 1995; Stefanova et al., 2003]. Specific features not observed in Zimmerman–Laband syndrome include deafness and optic atrophy, while hepatosplenomegaly is not part of the DOOR phenotype. Fetal hydantoin syndrome shares features with DOOR syndrome, most notably coarse facial features and nail dysplasia. However, growth retardation, deafness, and optic nerve atrophy are not observed. Fetal alcohol syndrome shares features with DOOR syndrome including nail dysplasia and hand anomalies (particularly terminal digit anomalies) [Wang et al., 2002]. The facial features, however, are distinct. Those with fetal alcohol syndrome are hypoteloric with a smooth philtrum, unlike the facial features of DOOR syndrome which includes hypertelorism and a long, prominent philtrum.

Recognizing a wide-ranging severity of neurologic manifestations in DOOR syndrome, Rajab et al. [2000] suggested a tentative classification schema based on

presence or absence of 2-oxoglutaric aciduria into DOOR type I and type II. In Rajab's classification, type I is characterized by increased 2-oxoglutarate, seizures before 6 months and a progressive course leading to blindness as well as early mortality, whereas in his second group, urinary 2-oxoglutarate levels are normal, clinical course is milder and does not show severe neurologic deterioration or blindness. Our literature review suggests that a divide between type I and type II DOOR is not clear. Only 5/14 patients with DOOR syndrome have been shown to have normal urinary 2-oxoglutarate [Lin et al., 1993; Bos et al., 1994; Felix et al., 2002], three of which appear to be severely affected [Felix, personal communication]; two had seizures in early infancy, all showed a progressive clinical course with increasing severity of seizures, and two died in childhood [Felix, personal communication]. In addition, variable expression exists within a single family; Qazi and Nangia reported a pair of siblings in which the brother was mildly affected and had a static clinical course, whereas the sister severe neurodevelopmental issues and regression of acquired milestones [Qazi and Nangia, 1984]. The schema of type I and type II DOOR syndrome is problematic for other reasons. Individuals with DOOR syndrome are demonstrated to have a fluctuating range of urinary 2-oxoglutarate throughout time. It has been noted that many single measurements in DOOR patients fall within the upper range of normal, even in those with previous elevations [Patton et al., 1987; Van Bever et al., 2007]. Thus, a single normal measurement of urinary 2-oxoglutarate, as performed in those cases reporting normal levels, should be considered insufficient in the workup of suspected DOOR syndrome [Lin et al., 1993; Bos et al., 1994; Felix et al., 2002]. Thus, a distinction between type I and type II DOOR syndrome does not hold true. Another explanation for the extensive interfamilial variability in neurodevelopment phenotype in DOOR syndrome may be the existence of differing severities of enzymatic defects. This further supports the understanding of DOOR syndrome as a neurometabolic disorder.

An autosomal recessive inheritance pattern for DOOR syndrome is highly suspected. A high frequency of consanguinity is observed in those families with affected children, 28% (9/32). Perhaps the strongest support for an autosomal recessive inheritance pattern of DOOR syndrome comes from Rajab et al. [2000] who described an Omani family with three children with DOOR syndrome born to double first cousins, as well as a fourth affected child in the same extended family, born to another pair of double first cousins. It should be noted, however, that exclusion criteria were chosen in this review such that those cases with other inheritance patterns were not included [Goodman et al., 1969; Moghadam and Statten, 1972].

Few attempts to identify prognostic markers have been made in DOOR syndrome. Rajab et al. [2000] suggested that early onset seizures (before 6 months) are a poor prognostic indicator. As early onset/high frequency of seizures are observed in cases without significant neurodevelopmental impairment [Cantwell, 1975; Sanchez et al., 1981; Qazi and Nangia, 1984], it appears that age of seizure onset is not of significant prognostic value. On the other hand, Rajab et al. [2000] also suggested that optic atrophy predicted a poor prognosis, an observation which appears to be valid [Hess et al., 1984; Eronen et al., 1985; Le Merrer et al., 1992; Rajab et al., 2000]. Additionally, we appreciated that complete absence of fingernails has been observed only in cases of early mortality, and thus may indicate a poor prognosis [Eronen et al., 1985; Le Merrer et al., 1992; Rajab et al., 2000].

When the diagnosis of DOOR syndrome is considered in an individual, we suggest that the following workup is indicated: hearing test, ophthalmologic exam, X-rays of the hands and feet, electroencephalogram, and brain CT and/or MRI, echocardiogram, screening abdominal ultrasound for renal abnormalities. The appropriate laboratory studies include karyotype analysis and urine 2-oxoglutarate (using multiple sequential samples until one is elevated). Other specialized tests that may be considered include VEP, ERG, EMG, and nerve conduction studies. As part of the long-term management, repeat ophthalmologic exams, hearing tests and EEGs may be appropriate.

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## REFERENCES

Bos CJM, Ippel PF, Beemer FA. 1994. DOOR syndrome: Additional case and literature review. Clin Dysmorphol 3:15–20.

Cantwell RJ. 1975. Congenital sensori-neural deafness associated with onycho-osteo dystrophy and mental retardation (D.O.O.R syndrome). Humangenetik 26:261–265.

Eronen M, Somer M, Gustafsson B, Holmberg C. 1985. New syndrome: A digito-reno-cerebral syndrome. Am J Med Genet 22:281–285.

Feinmesser M, Zelig S. 1961. Congenital deafness associated with onychodystrophy. Arch Otolaryng 74:507–508.

Felix TM, de Menezes Karam S, Della Rosa VA, Moraes AM. 2002. DOOR syndrome: Report of three additional cases. Clin Dysmorphol 11:133–138.

Fleck BJ, Pandya A, Vanner L, Kerkering K, Bodurtha J. 2001. Coffin-Siris syndrome: Review and presentation of new cases from a questionnaire study. Am J Med Genet 99:1–7.

Goodman RM, Lockareff S, Gwinup G. 1969. Hereditary congenital deafness with onychodystrophy. Arch Otolaryng 90:474–477.

Hess RO, Pecotte JK. 1984. Letter to the editor: Additional case report fo the DOOR syndrome. Am J Med Genet 19:401–405.

Laband PF, Habib G, Humphreys GS. 1964. Hereditary gingival fibromatosis: Report of an affected family with associated splenomegaly and skeletal and soft-tissue abnormalities. Oral Surg 17:339–351.

Le Merrer M, David A, Goutieres F, Briard ML. 1992. Digito-reno-cerebral syndrome: Confirmation of Eronen syndrome. Clin Genet 42:196–198.

Lin HJ, Kakkis ED, Eteson DJ, Lachman RS. 1993. DOOR syndrome (Deafness, onycho-osteodystrophy, and mental retardation): A new patient and delineation of neurologic variability among recessive cases. Am J Med Genet 47:534–539.

Moghadam H, Statten P. 1972. Hereditary sensorineural hearing loss associated with onychodystrophy and digital malformations. Canad Med Assoc J 107:310–311.

Nevin NC, Thomas PS, Calvert J, Reid MM. 1982. Deafness, onycho-osteodystrophy, mental retardation (DOOR) syndrome. Am J Med Genet 13:325–332.

Patton MA, Krywawych S, Winter RM, Brenton DP, Baraitser M. 1987. DOOR syndrome (deafness, onycho-osteodystrophy, and mental retardation): Elevated plasma and urinary 2-oxoglutarate in three unrelated patients. Am J Med Genet 26: 207–215.

Qazi QH, Nangia BS. 1984. Abnormal distal phalanges and nails, deafness, mental retardation, and seizure disorder: A new familial syndrome. J Pediatr 104:391–394.

Qazi QH, Smithwick EM. 1970. Triphalangy of thumbs and great toes. Amer J Dis Child 120:255–257.

Rajab A, Riaz A, Paul G, Al-khusaibi S, Chalmers R, Patton MA. 2000. Further delineation of the DOOR syndrome. Clin Dysmorphol 9:247–251.

Reardon W, Boyd S, Pitt MC, Wilson J, Winter RM. 1994. Disordered peripheral nerve conduction in DOOR(S) syndrome. Neuropediatrics 25:33–35.

Sadoun E, Hansel S, Challier P, Bijaoui G. 1989. Onychodystrophy, sensory and mental deficits with neonatal seizures (DOORS syndrome). Arch Fr Pediatr 46:465.

Sanchez O, Mazas JJM, Oritz de DeMatos I. 1981. The deafness, onycho-osteo-dystrophy, mental retardation syndrome. Two new cases. Hum Genet 58:228–230.

Stefanova M, Atanassov D, Krastev T, Fuchs S, Kutsche K. 2003. Zimmerman-Laband syndrome associated with a balanced reciprocal translocation t(3;8)(p21.2;q24.3) in mother and daughter: Molecular cytogenetic characterization of the breakpoint regions. Am J Med Genet Part A 117A:289–294.

Surendran S, Michals-Matalon K, Krywawych S, Qazi QH, Tuchman R, Rady PL, Tyring SK, Matalon R. 2002. DOOR syndrome: Deficiency of E1 component of the 2-oxogluturate dehydrogenase complex. Am J Med Genet 113:371–374.

Szabo L, Kocsis K, Hollody K, Soroncz M, Erwa W, Andits M. 2004. DOOR (deafness, onychodystrophy, osteodystrophy, mental retardation) syndrome. Orvil Hetil 145:1183–1187.

Thomas PS, Nevin NC. 1982. Radiologic findings in DOOR syndrome. Ann Radiol (Paris) 25:54–58.

Thornton CM, Magee AC, Thomas PS, Feakins R, Nevin NC, O'Hara MD. 1994. Congenital heart disease and urinary tract abnormalities in two siblings with DOOR syndrome. Pediatr Path 14:797–803.

Van Bever Y, Balemans W, Duval EL, Jespers A, Eyskens F, van Hul W, Courtens W. 2007. Exclusion of OGDH and BMP4 as candidate genes in two siblings with autosomal recessive DOOR syndrome. Am J Med Genet Part A 143A:763–767.

Van Buggenhout GJMC, Brunner HG, Trommelen JCM, Hamel BCJ. 1995. Zimmerman-Laband syndrome in a patient with severe mental retardation. Genet Counsel 6:321–327.

Walbaum R, Fontaine G, Lienhardt J, Piquet JJ. 1970. Familial deafness with osteo-onycho-dysplasia. J Genet Hum 18:101–108.

Wang R, Martinez-Frias ML, Graham JM. 2002. Infants of diabetic mothers are at increased risk for the oculo-auriculo-vertebral sequence: A case-based and case-control approach. J Pediatr 141:611–617.

Winter RM. 1992. Eronen syndrome identical with DOOR syndrome? Clin Genet 42:196–198.