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ORIGINAL ARTICLE

Neck masses due to internal jugular vein phlebectasia: Frequency in Menkes disease and literature review of 85 pediatric subjects

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Abstract

Classic Menkes disease is a rare X-linked recessive disorder of copper metabolism caused by pathogenic variants in the copper transporter gene, *ATP7A*. Untreated affected individuals suffer failure to thrive and neurodevelopmental delays that begin at 6–8 weeks of age and progress inexorably to death, often within 3 years. Subcutaneous injections of Copper Histidinate (US Food and Drug Administration IND #34,166, Orphan product designation #12-3663) are associated with improved survival and neurological outcomes, especially when commenced within a month of birth. We previously identified internal jugular vein phlebectasia (IJP) in four Menkes disease subjects. This feature and other connective tissue abnormalities appear to be consequences of deficient activity of lysyl oxidase, a copper-dependent enzyme. Here, we report results from a prospective study of IJP based on 178 neck ultrasounds in 66 Menkes subjects obtained between November 2007 and March 2018. Nine patients met the criterion for IJP (one or more cross-sectional area measurements exceeding 2.2 cm^2) and five subjects had clinically apparent neck masses that enlarged over time. Our prospective results suggest that IJP occurs in approximately 14% (9/66) of Menkes disease patients and appears to be clinically benign with no specific medical or surgical actionability. We surveyed the medical literature for prior reports of IJP in pediatric subjects and identified 85 individuals and reviewed the distribution of this abnormality by gender, sidedness, and underlying etiology. Taken together, Menkes disease accounts for 16% (15/94) of all reported IJP individuals. Neck masses from IJP represent underappreciated abnormalities in Menkes disease.

KEYWORDS

ATP7A, copper, jugular veins, Menkes Kinky Hair syndrome, phlebectasia, protein-lysine 6-oxidase

1 | INTRODUCTION

Menkes disease is a rare, X-linked disorder caused by a diverse range of variants in the gene for copper transport protein ATP7A (Kaler, 2011). Classic clinical signs include *pili torti* ("kinky hair"), delayed physical growth, cerebral and cerebellar atrophy, and dysmyelination. Affected infants appear healthy at birth and develop normally for 2–3 months of age, but then display loss of neurodevelopmental milestones, and premature mortality, often by 3 years of age (Kaler, 2013).

Other associated clinical manifestations include dysautonomia, hypotonia, seizures, failure to thrive, reduced pigmentation, and connective tissue abnormalities, such as bladder diverticula, skin and joint laxity, generalized vascular tortuosity, gastric polyps, and pectus

excavatum. These features reflect deficiencies of enzymes that normally require copper as a cofactor, including dopamine-beta-hydroxylase (DBH), cytochrome c oxidase (CCO), superoxide dismutase (SOD), tyrosinase, and lysyl oxidase (LO). Of these, LO appears to have an influential role in connective tissue development (Nishioka, Eustace, & West, 2012; Price, Ravindranath, & Kaler, 2007).

Internal jugular phlebectasia (IJP) in infants and children presents as a nonpainful, nonpulsatile, compressible mass on the neck that enlarges when the patient performs a Valsalva maneuver, coughs, or cries (Figure 1). First reported by Harris (1928), who diagnosed it as a congenital venous cyst, IJP represents a venous dilation without tortuosity, while another frequent label is venous aneurysm (Baker, Ingraham, Fine, Iyer, & Monroe, 2017; Gilbert, Greenberg, Brown, & Puranik, 1972; Paleri & Gopalakrishnan, 2001). Differential diagnosis includes external laryngocele or diverticulum, pharyngocele, superior mediastinal tumor, and branchial cyst (Bowdler & Singh, 1986; Paleri & Gopalakrishnan, 2001).

Most authors consider IJP to be congenital, which dovetails with more frequent diagnosis in childhood than adulthood (Al Tamami & Al Macki, 2015; Bhattacharya, Endrakanti, & Kumar, 2017). Symptoms are often observed by patients and families for months or years before diagnosis by a clinician (Al-Dousary, 1997; Baker et al., 2017; Shimizu, Takagi, Yoshio, Takeda, & Matsui, 1992). Patients frequently reported a gradual increase as the child grows, and phlebectasias are more common on the right than the left (Bowdler & Singh, 1986; Paleri & Gopalakrishnan, 2001).

The current standard for evaluating and quantifying phlebectasia is ultrasound, often accompanied by Doppler color studies, which are cost-effective, noninvasive, and accurate (Eksioglu, Senel, Cinar, & Karacan, 2013; Malik, Kumari, & Murthy, 2015; Sundaram, Menon, Thingnum, & Rao, 2016). Historically, diagnosis was also based on magnetic resonance imaging, computed tomography, and other radiologic studies, such as direct dye injection (Al Tamami & Al Macki, 2015; Paleri & Gopalakrishnan, 2001). Similarly, during early decades of treatment, surgery was more frequent; currently, most cases are handled conservatively when phlebectasias are not accompanied by comorbidities, though surgery may be chosen for cosmetic reasons (Al Tamami & Al Macki, 2015; Bhattacharya et al., 2017).

In 2007, we reported three Menkes disease infants who developed large unilateral neck masses due to IJP between the ages of 7 and 17 months (Price et al., 2007). None of these three patients suffered any known adverse clinical consequences related to this finding. One remains alive at age 14 years following 3 years of early Copper Histidinate treatment (Patient #3), one died at age 11 years and 9 months following 3 years of early Copper Histidinate treatment (Patient 2), and one died at age 8 years and 6 months following 3 years of early Copper Histidinate treatment.

Here, we present a comprehensive prospective study of IJP in Menkes disease. In addition, we present a detailed literature review of 85 reported pediatric patients with IJP.

2 | MATERIALS AND METHODS

2.1 | Study population

Menkes disease patients were referred from clinical geneticists, neurologists, and pediatricians to participate in clinical trials of Copper Histidinate for Menkes disease (ClinicalTrials.gov identifiers NCT00001262 and NCT0081785). The studies were approved by Institutional Review Boards of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke, and conducted in conformity with the Declaration of Helsinki and US Federal Policy for the Protection of Human Subjects. Informed consent was obtained from the parents of all subjects.

Based on *ATP7A* molecular analysis, the subjects had a variety of variant types, including chromosomal abnormalities, copy number variants, missense variants, nonsense variants, and splice site variants. Further demographic characteristics of 66 patients are described in Table 1.

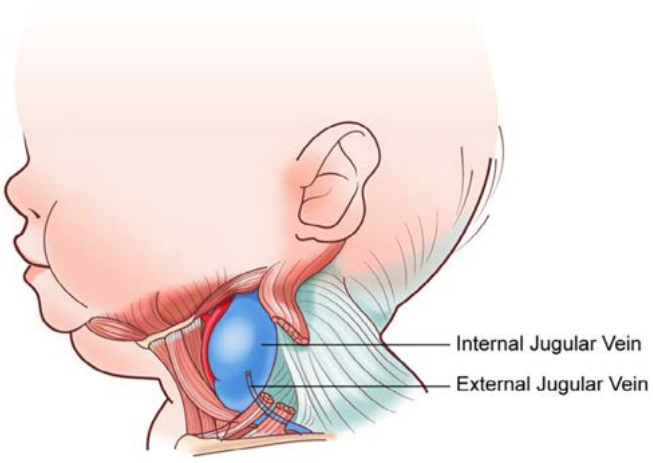

FIGURE 1 Left side neck vasculature in a pediatric patient showing internal jugular vein phlebectasia

TABLE 1 Demographics of Menkes disease patients (*N* = 66)

	N	%
Age of patient at first IJ measurement		
<6 months	23	35%
6–12 months	30	45%
13–24 months	7	11%
>24 months	6	9%
Sex		
Female	1	2%
Male	65	98%
Phlebectasia frequency		
No phlebectasia	57	86%
Phlebectasia	9	14%

2.2 | Variant analysis

The *ATP7A* locus in subjects was screened by multiplex PCR and automated sequencing, using genomic DNA from white blood cells, as previously described (Liu, McAndrew, & Kaler, 2015).

2.3 | Ultrasound procedure

All IJ ultrasounds were performed in the Radiology Department at the National Institutes of Health Clinical Center using a GE Logiq E9 ultrasound instrument (or equivalent) with a linear high-resolution probe. Measurements of the dimensions upper, mid, and lower portion of the left and right IJ vein were reported in centimeters.

2.4 | Calculation of cross-sectional area

Internal jugular vein cross-sectional area (CSA) was calculated using the formula for the area for an ellipse: $A_{ellipse} = \pi/4 \times$ major axis $\times$ minor axis, using the mid-portion measurement for both right and left sides. Eksioglu et al. (2013) concluded that a cutoff of 2.2 cm^2 for the CSA during Valsalva maneuver was useful in diagnosing pediatric phlebectasia.

2.5 | Literature review

References were compiled from PubMed and the National Library of Medicine in Bethesda, Maryland. Search terms were limited to articles in English and included combinations of the following: Menkes, internal, jugular, phlebectasia, pediatric, and aneurysm. Additional case studies were found in reference lists and older literature reviews. Articles that did not provide individual patient and phlebectasia characteristics (such as sex, side, and age at diagnosis) were not included.

3 | RESULTS

3.1 | IJ measurements of Menkes disease patients

We compiled IJ CSAs for 66 Menkes disease patients. Figure 2 summarizes 178 pairs of measurements according to left and right sides. The mean for all measurements, including outliers, was 1.002 cm^2 (±1.729 cm^2 SD, $N = 356$).

3.2 | Menkes disease patients with IJP

Using a threshold of mid-IJ CSA equal to 2.2 cm^2, we found nine Menkes disease patients with phlebectasia. Table 2 summarizes characteristics and ATP7A variant data for these nine patients, as well as for six other Menkes patients from the literature. Since large deletions, nonsense, splice junction, and missense ATP7A variants were all noted, no clear correlation between ATP7A variant severity and the incidence or degree of IJP was evident. Serial ultrasound images for two subjects who presented with unilateral IJP and developed bilateral IJP over time are shown in Figure 3.

Five of the nine subjects (Patients 1, 3, 7, 8, and 9) also had clinically visible neck bulges, as detailed below in the narrative case studies.

Patient 1. This patient's initial ultrasound IJ measurements were unremarkable. Abnormal measurements were found at his third and fourth protocol visits at 17 months and 31 months, respectively. At 17 months, ultrasound-measured right mid-IJ area was 6.099 cm^2, and the same location was 5.22 cm^2 at 31 months. Phlebectasia treatment was conservative.

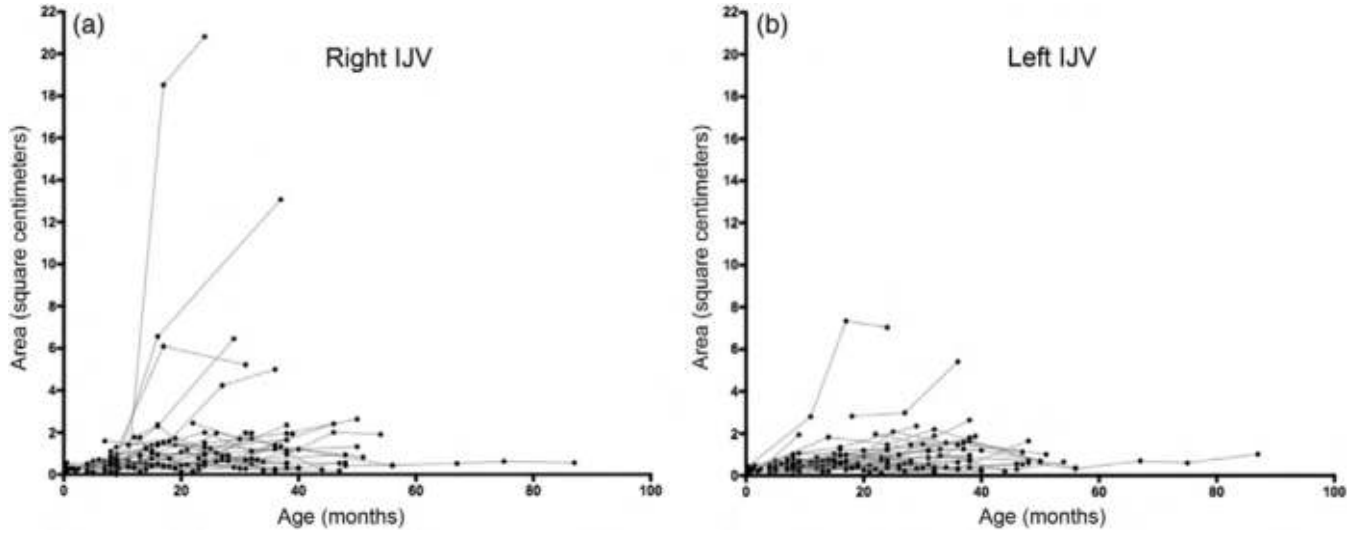

FIGURE 2 Scatter plots of mid-IJ cross-sectional area (in cm^2) of Menkes disease patients compared to age. (a) and (b) contain data from right- and left-sided IJs, respectively. Lines connect data points from the same patient at different visits

TABLE 2 Summary of characteristics for 15 Menkes disease patients with IJV phlebectasia

Case number	Chronologic age at Menkes diagnosis	Age when phlebectasia first noted	Age at death	Sex	Side	ATP7A variant	Ref
1	19 d	17 m	39 m	Male	Right	NM 000052.7 c.1639C>T Arg547term	TR
2	13 m	22 m	n/a	Male	Right	NM 000052.7 c.2916 +3 del 4 IVS14 DS +3, del 4	TR
3	8 d	16 m	n/a	Male	Bilateral	Del exon 1	TR
4	8 m	16 m	32 m	Female	Right	NM 000052.7 3445 del C Gln1149Lys fs*13	TR
5	6 w	38 m	n/a	Male	Bilateral	NM 000052.7 c.2627-1g>a IVS12 SA −1, g>a	TR
6	7 m	46 m	n/a	Male	Right	NM 000052.7 c.3753 del T Leu1252term	TR
7	1 w	11 m	n/a	Male	Bilateral	Del exon 1	TR
8	2 w	16 m	n/a	Male	Right	Del exon 13–14	TR
9	2 w	6 m	n/a	Male	Bilateral	Del exon 2–14	TR
10	28 d	11 m	14 m	Male	Right	NM 000052.7 c.3111G>T Lys1037Asn; also affects splicing: IVS15 SD −1, G>T	Grange 2005
[a]11	6 w	16 m	8.5 y	Male	Right	NM 000052.7 c.2499 −1,g>a IVS11,SA −1,g>a	Price 2007
[a]12	3 w	7 m	11.75 y	Male	Left	NM 000052.7 c.2179G>C Gly727Arg	Price 2007
[a]13	Prenatal	17 m	n/a	Male	Left	Del exons 20–23	Price 2007
14	6 w	9 m	13 m	Male	Bilateral	NM 000052.7 c.1497C>A Cys499term	Bonnet 2015
15	3 m	20 m	36 m	Male	Bilateral	NM 000052.7 c.1012 del G Val338Tyr fs*31	Bonnet 2015

Abbreviations: d, day; m, month; n/a, not applicable; SA, splice acceptor; SD, splice donor; TR, this report; w, week; y, year.
[a]Previously unreported or updated details for three NCT00001262 subjects from Price et al. 2005 are shown here.

Patient 3. This patient's ultrasound IJ measurements showed some enlargement at 16 months (2.3 cm^2 on the right in contrast to 1.352 cm^2 on the left). His right-sided measurements worsened during study visit four at the age of 29 months (6.458 cm^2 on the right, 2.355 cm^2 on the left). His phlebectasia was managed conservatively and measurements continued to be abnormal at 29 months old. This patient is now 7 years old and his phlebectasia continues to be asymptomatic.

Patient 7. While the left CSA measurement at this patient's 11-month visit (2.803 cm^2) exceeded the published threshold for phlebectasia, this patient's parents first reported expanding bilateral neck bulges at his 17-month visit (18.526 cm^2 on the right and 7.348 cm^2 on the left). Both family and clinicians noticed an increase in the bulging while the patient was crying. Slow blood flow in the dilated veins was noted during the ultrasound examination. At a 24 month follow-up, the CSA had increased to 20.818 cm^2 on the right and 7.034 cm^2 on the left. These measurements are approximate because the vein exceeded the transducer field of view. His phlebectasia has been conservatively managed and will continue to be monitored.

Patient 8. At 2 weeks of age, this patient's IJ measurements were within normal limits, though the radiologist noted findings that were

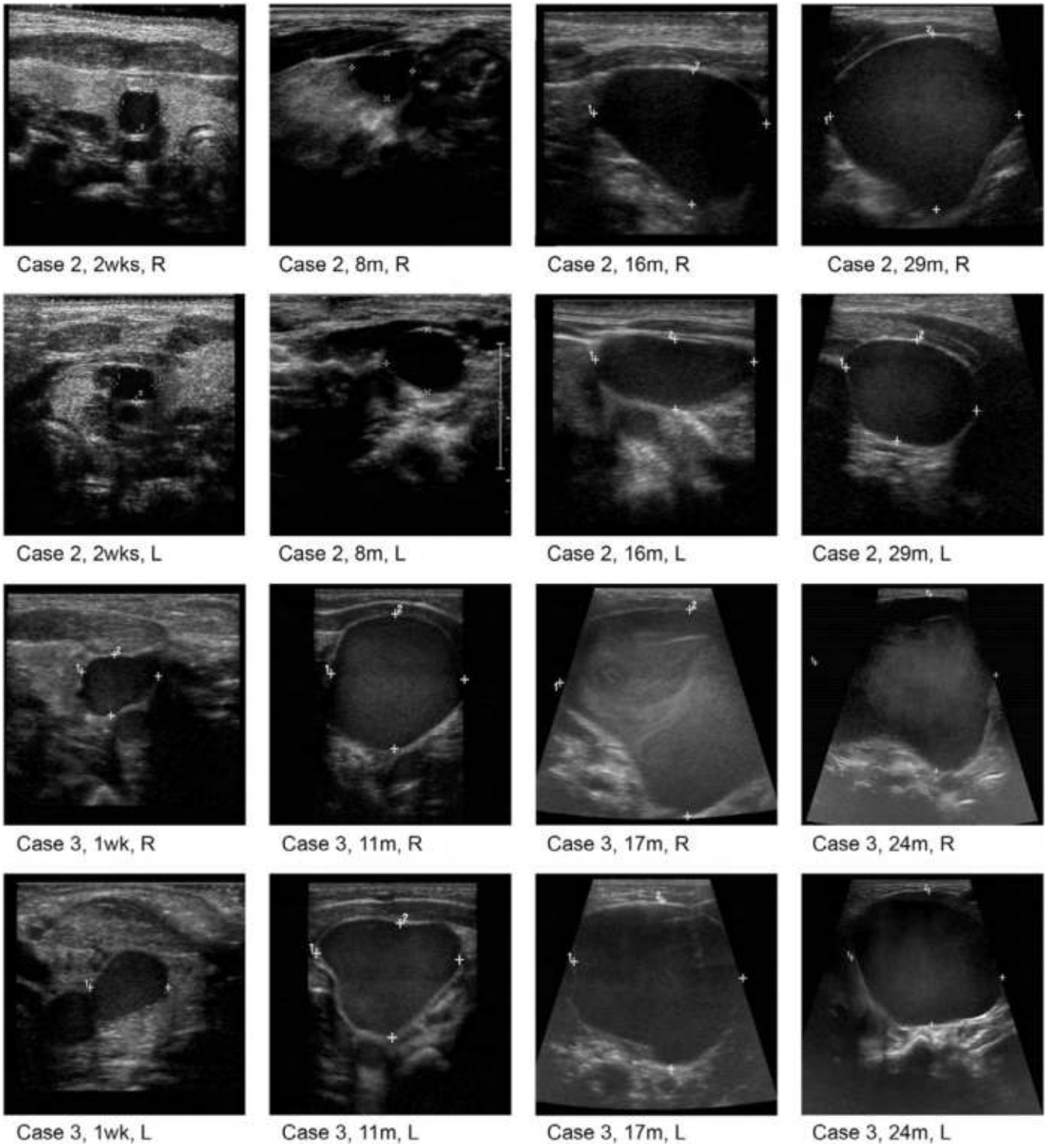

FIGURE 3 Serial left and right mid-IJ ultrasound images of Case Studies 2 and 3 with ages noted. For Case 3 at 17 and 24 months of age, the cross-section exceeded the transducer area

compatible with bilateral slow flow. At age 16 months he had a right neck mass and the right IJ area was (6.563 cm^2) in contrast to a left IJ at 0.989 cm^2. Phlebectasia management has been conservative and he will continue to be monitored.**Patient 9**. This patient's first visit was at 6 months of age. Clinical observations included bilateral jugular vein distention, but ultrasound measurements are not detailed enough to calculate CSA. At 18 months old, he had right—but not left—jugular vein phlebectasia (2.826 cm^2 and 1.6 cm^2, respectively). By 27 months old, he had bilateral phlebectasia, 4.239 cm^2 on the right and 2.983 cm^2 on the left. At his final protocol visit at 3 years old, both CSAs were above 5 cm^2: 5.001 cm^2 on the right and 5.416 cm^2 on the left. Management throughout has been conservative.

TABLE 3 Pediatric internal jugular vein phlebectasia in English literature (*N* = 85)

#	Author	Year	Age	Sex	Side	Duration before diagnosis[1]	Causes/clinical characteristics	Diagnostic evaluation	Treatment	Outcome
1	Harris	1928	5 m	F	R	4 w prior	Cyanosis, coughing, voice hoarseness	Surgical exploration	Surgical	Died during surgery
2	Zukschwerdt (in Gerwig)	1929	9 y	F	R	Not reported	IJ duplication	Not reported	Surgical	Not reported
3	Gerwig Jr. (1952)	1952	12 y	M	R	7 y prior	No known cause	X-ray/surgical exploration	Surgical	No complications at 4 y
4	Pataro et al. (Case A, in Garrow, Kirschtein, & Som, 1964)	1961	5 y	M	R	Not reported	Not reported	Not reported	Surgical	Not reported
5	Pataro et al. (Case B, in Garrow et al.)	1961	7 y	M	R	Not reported	Not reported	Clinical grounds	Conservative	Not reported
6	Garrow et al.	1964	13 y	F	L	6 m prior	No known cause	Surgical exploration	Surgical	No complications at 2 y
7	Gilbert et al. (Case A)	1972	3 y	M	R	18 m prior	Not reported	Radiography with contrast	Conservative	Not reported
8	Gilbert et al. (Case B)	1972	30 m	F	R	2 m prior	Right neck abscess and cyst	Radiography with contrast	Surgical	Not reported
9	Gordon et al. (Case A)	1976	6 y	M	R	4 y prior	Gradual increase	Radiography with contrast	Surgical	Not reported
10	Gordon et al. (Case B)	1976	2 y	F	R	17 m prior	Gradual increase	Radiography with contrast	Surgical	Not reported
11	Gordon et al. (Case C)	1976	10 y	M	R	4 y prior	Not reported	Radiography with contrast	Surgical	Not reported
12	LaMonte et al. (Case A)	1976	6 y	M	R	4 y prior	Noticed by family after croup	Radiography with contrast	Conservative	Not reported
13	LaMonte et al. (Case B)	1976	20 y	F	R	12 y prior	Dyspnea	Radiography with contrast	Conservative	Not reported
14	Mallik (1977)	1977	7 y	M	R	2 y prior	Gradual increase	Surgical exploration	Surgical	No complications at 2 w
15	Passariello et al. (1979) (Case A)	1979	5 y	M	R	3 m prior	Not reported	Radiography with contrast	Surgical	Not reported
16	Pasariello et al. (Case B)	1979	6 y	F	R	2 y prior	Gradual increase	Radiography with contrast	Surgical	Not reported
17	Pasariello et al. (Case C)	1979	9 y	M	R	2 m prior	Concurrent external jugular veindilation	Radiography with contrast	Surgical	Not reported
18	Pasariello et al. (Case D)	1979	4 y	M	R	Not reported	Not reported	Radiography with contrast	Conservative	Not reported
19	Danis (Case A)	1982	22 m	F	L	4 m prior	Inguinal hernia	Surgical exploration	Surgical	No complications at 4 y
20	Danis (Case B)	1982	9 y	F	L	6 m prior	Gradual increase	Surgical exploration	Surgical	No complications at 4 y
21	Danis (Case C)	1982	4 y	M	L	8 m prior	Gradual increase	Surgical exploration	Surgical	No complications at 4 y
22	Stevens, Fried, and Hood Jr. (1982)	1982	10 y	M	R	2 y prior	Lymphoreticular hyperplasia	Ultrasound	Conservative	Not reported

TABLE 3 (Continued)

#	Author	Year	Age	Sex	Side	Duration before diagnosis[1]	Causes/clinical characteristics	Diagnostic evaluation	Treatment	Outcome
23	Leung, Hampson, Singh, and Carr (1983)	1983	9 y	M	B	6 y prior	No known cause	Ultrasound (quantified)	Conservative	Not reported
24	Yashiro and Iio (1984) (Case A)	1984	10 y	M	R	Not reported	No known cause	Radiography with contrast	Conservative	Not reported
25	Yashiro et al. (Case B)	1984	5 y	M	R	Not reported	Not reported	Radiography with contrast	Conservative	Not reported
26	Bowdler et al.	1986	6 y	M	R	3.5 y prior	Gradual increase	Radiography with contrast	Conservative	No complications at 8 y
27	Hughes, Qureshi, and Galloway (1988)	1988	3 y	M	L	1 y prior	Not reported	Radiography with contrast	Surgical	Not reported
28	Nwako, Agugua, Udeh, and Osuorji (1989)	1989	5 y	M	R	1 y prior	Recurrent fever, weight loss for 1 y. Neonatal exchange transfusion.	Surgical exploration	Surgical	No complications at 6 m
29	Yokomori, Kubo, Kanamori, Takemura, and Yamamoto (1990) (Case A)	1990	6 y	M	R	4 m prior	Brother also has IJP	Ultrasound	Surgical	No complications at 8 m
30	Yokomori et al. (Case B)	1990	4 y	M	R	2 m prior	Brother also has IJP	Ultrasound	Surgical	No complications postop
31	Dhillon and Leong (1991)	1991	8 y	M	R	1 y prior	Not reported	Ultrasound and radiography with contrast	Conservative	Not reported
32	Kuo et al. (1992)	1992	6 y	F	R	3 y prior	No known cause	Radiography with contrast	Surgical	No complications at 2 y
33	Shimizu et al.	1992	20 y	F	L	16 y prior	No known cause	Ultrasound and radiography with contrast	Conservative	Not reported
34	Walsh, Murty, and Bradley (1992)	1992	5 y	M	B	3 m prior	Not reported	Ultrasound (quantified)	Conservative	No complications at 18 m
35	Balik et al. (1993)	1993	8 y	M	R	1 y prior	Not reported	Ultrasound and radiography with contrast	Surgical	Not reported
36	Walsh, Lannigan, McGlashan, and Bowdler (1993)	1993	4 y	M	B	2 y prior	Not reported	Radiography with contrast	Conservative	No complications at 5 y
37	Gendeh, Dhillon, and Hamzah (1994)	1994	4 y	M	B	2 m prior	No known cause	Ultrasound	Conservative	No complications at 2 y
38	Inci et al.	1995	8 y	M	R	Not reported	Right-sided Horner's syndrome	Radiography with contrast	Conservative	No complications at 6 m
39	Hussein and Trowitzsch (1996)	1996	2 m	M	R	N/A	Premature (born at 32 weeks)	Ultrasound	Not reported	Not reported
40	Al-Dousary	1997	11 y	M	R	2 m prior	No known cause	Ultrasound	Conservative	No complications at 21 m

(Continues)

TABLE 3 (Continued)

#	Author	Year	Age	Sex	Side	Duration before diagnosis[1]	Causes/clinical characteristics	Diagnostic evaluation	Treatment	Outcome
41	Gurpinar, Kiristioglu, and Dogruyol (1999)	1999	5 y	M	R	6 m prior	No known cause	Ultrasound and radiography with contrast	Surgical	No complications at 6 m
42	Indudharan, Quah, and Shuaib (1999)	1999	7 y	M	R	6 m prior	Enlarged tonsils and adenoids-leading to adenotonsilectomy	Ultrasound and radiography with contrast	Conservative	Reduction in size at 24 mo
43	Sander et al. (Case A)	1999	14 y	F	R	Not reported	Gradual increase	Ultrasound	Surgical	No complications at 6 y
44	Sander et al. (Case B)	1999	12 y	M	R	Not reported	Gradual increase	Ultrasound	Surgical	No complications at 6 y
45	Sander et al. (Case C)	1999	3 y	M	L	Not reported	Gradual increase	Ultrasound	Surgical	No complications at 5 y
46	Sander et al. (Case D)	1999	3 y	F	R	Not reported	Gradual increase	Ultrasound	Surgical	No complications at 5 y
47	Sander et al. (Case E)	1999	4 y	F	L	Not reported	Gradual increase, difficulty swallowing	Ultrasound	Surgical	No complications at 3 y
48	Sander et al. (Case F)	1999	5 y	M	R	Not reported	Gradual increase	Ultrasound	Surgical	No complications at 3 y
49	Sander et al. (Case G)	1999	7 y	M	R	Not reported	Gradual increase, vocal changes	Ultrasound	Surgical	No complications at 10 m
50	Sander et al. (Case H)	1999	8 y	M	R	Not reported	Gradual increase, vocal changes	Ultrasound	Surgical	No complications at 6 m
51	Kwok, Lam, and Ng (2000) (Case A)	2000	10 y	M	R	3 m prior	Asthma	Ultrasound and radiography with contrast	Conservative	Not reported
52	Kwok et al. (Case B)	2000	8 y	M	R	1 y prior	Asthma	Ultrasound	Conservative	Not reported
53	Kwok et al. (Case C)	2000	8 y	F	R	2 y prior	Asthma, inguinal hernia	Ultrasound	Conservative	Not reported
54	Paleri et al. (Case A)	2001	10 y	F	R	2 y prior	No known cause	Ultrasound	Conservative	No complications at 1 y
55	Paleri et al. (Case B)	2001	3 y	M	R	Not reported	No known cause	Ultrasound	Conservative	No complications at 6 m
56	Reed and Grewal (2001)	2001	3 y	M	L	Not reported	Not reported	Ultrasound (quantified)	Conservative	No complications postop
57	Rossi et al.	2001	2 y	F	R	New when diagnosed	Bilateral partial duplication of IJV	Ultrasound and MRA	Conservative	Not reported
58	Erdem, Erdem, and Camuzcuoglu (2002) (Case A)	2002	6 y	F	R	4 y prior	Gradual increase	Ultrasound	Conservative	No complications at 1 y
59	Erdem et al. (2002) (Case B)	2002	10 y	F	R	5 y prior	Asthma	Ultrasound	Conservative	No complications at 9 m
60	Erdem et al. (2002) (Case C)	2002	14 y	F	R	N/A	Euthyroid goiter	Ultrasound	Conservative	No complications at 9 m

TABLE 3 (Continued)

#	Author	Year	Age	Sex	Side	Duration before diagnosis[1]	Causes/clinical characteristics	Diagnostic evaluation	Treatment	Outcome
61	Yilmaz (2003)	2003	15 y	F	R	Not reported	No known cause	Ultrasound and radiography with contrast	Conservative	No complications at 2 y
62	Fishman et al.	2004	2 y	M	R	2 y prior (birth)	Neck varices, external jugular vein aneurysm	Ultrasound and radiography with contrast	Surgical	Asymptomatic postop
63	Rajendran, Vasu, Regi George, Anjay, and Anoop (2004)	2004	10 y	F	R	4 y prior	No known cause	Ultrasound (quantified)	Conservative	Not reported
64	Collins and Zalzal (2005)	2005	5 y	M	R	1 y prior	No known cause	Radiography with contrast (quantified)	Conservative	Not reported
65	Grange et al.	2005	14 m	M	R	3 m prior	Menkes disease	Ultrasound and MRI	Conservative	Died from respiratory complications of Menkes
66	Ferreira (2007) (Case A)	2007	5 y	F	B	Not reported	No known cause	Ultrasound	Conservative	Not reported
67	Ferreira et al. (Case B)	2007	4 y	M	B	Not reported	Bilateral but asymmetric: Left bigger than right	Radiography with contrast	Conservative	Not reported
68	Padmanabhan, Vaishali, and Indudharan (2007)	2007	15 y	F	R	Since birth	Paroxysmal cough 3 mo prior	Ultrasound (and radiography with contrast	Surgical	No complications at 2 y
69	Price et al. (Case A)	2007	16 m	M	R	1 m prior	Menkes disease	Ultrasound and MRI	Conservative	No complications at 21 m
70	Price et al. (Case B)	2007	7 m	M	L	N/A	Menkes disease	Ultrasound	Conservative	No complications at 17 m
71	Price et al. (Case C)	2007	17 m	M	L	N/A	Menkes disease	MRA and radiography with contrast	Conservative	No complications at 2 m
72	Souza, Lima, and Duprat (2008)	2008	10 y	F	R	10 y prior (birth)	Cervical venous anatomic abnormalities, atrophy of sternomastiod muscle	Ultrasound and radiography with contrast	Conservative	Not reported
73	Srivastava, Gangopadhyay, Sharma, and Jarman (2008)	2008	10 y	M	R	6 y prior	Not reported	Ultrasound	Conservative	No complications at 1 y
74	Chang, Lee, Wang, and Chiou (2010)	2010	8 y	F	R	3 y prior	Tenderness	Ultrasound with MRI	Surgical	No complications at 6 m
75	El Fakiri et al. (2011)	2011	6 y	M	R	2 y prior	No known cause	Radiography with contast	Conservative	No complications at 20 m
76	Chakraborty et al. (2013)	2013	7 y	F	R	1 y prior	Gradual increase, vocal changes	Radiography with contrast	Conservative	Not reported
77	Nagata et al. (2013)	2013	10 y	M	R	Not reported	No known cause	Ultrasound and radiography with contrast	Not reported	Not reported

(Continues)

TABLE 3 (Continued)

#	Author	Year	Age	Sex	Side	Duration before diagnosis[1]	Causes/clinical characteristics	Diagnostic evaluation	Treatment	Outcome
78	Awasthy, Khandelwal, and Iyer (2016)	2014	1 m	M	L	N/A	Large thrombus, no change with Valsalva	Ultrasound and radiography with contrast	Surgical	No complications at 1 y
79	Al-Tamani et al.	2015	10 y	M	R	4 y prior	No known cause	Radiography with contrast	Not reported	Not reported
80	Bonnet et al. (Case A)	2015	9 m	M	B	N/A	Menkes disease	Ultrasound and radiography with contrast	Conservative	Venous thrombosis. Died from respiratory complications of Menkes
81	Bonnet et al. (Case B)	2015	3 y	M	B	2 y prior	Menkes disease	Ultrasound	Conservative	Death during admission for respiratory distress
82	Malik et al.	2015	8 y	M	R	2 y prior	Gradual increase, intracranial extension	Ultrasound and radiography with contrast	Conservative	Not reported
83	Sundaram et al. (2016)	2016	7 m	M	R	3 m prior	Dysphagia	Ultrasound and radiography with contrast	Surgical	No complications at 9 m
84	Baker et al. (2017)	2017	3 m	M	L	3 m prior (birth)	No known cause	Ultrasound, MRI, and radiography with contrast	Surgical	No complications at 18 m
85	Bhattacharya et al.	2017	7 y	M	R	N/A	No known cause	Ultrasound and MRI	Conservative	Not reported

3.3 | Case studies from literature review

In Table 3, 85 individuals with pediatric phlebectasia reported in the English language medical literature to date are presented. Two patients were diagnosed as 20-year-old adults but they reported symptom onset dating 8 and 4 years of age.

Of the 85 reported individuals, only Menkes disease (6 patients), voice hoarseness (4 patients), and asthma (4 patients) were comorbidities affecting more than two patients. Some presentations could be categorized by their physical obstruction or compression of adjacent neck structures: voice hoarseness, paroxysmal coughing, and Horner's syndrome only appear in a few cases each (Harris, 1928; Inci, Bertan, Kansu, & Cila, 1995; LaMonte, Walker, & Moran, 1976). One commonality appears to be congenital malformations that manifest as venous duplications (Rossi & Tortori-Donati, 2001), hernias (Danis, 1982), and non-IJ aneurysms (Fishman, DeRowe, & Singhal, 2004). Table 4 summarizes characteristics of the case studies in the literature in comparison to the nine newly reported Menkes disease patients from this report.

4 | DISCUSSION

This study represents the first comprehensive evaluation of IJP in Menkes disease, a X-linked recessive disorder of human copper transport. Our results indicate that IJP occurred in approximately 14% (9/66) of this sizable cohort, and in six other Menkes patients reported previously (Bonnet et al., 2015; Grange et al., 2005; Price et al., 2007). The activity of the copper-dependent enzyme, lysyl oxidase (LO), is known to be reduced in subjects with Menkes disease (Gacheru et al., 1993; Kaler, 2011; Royce, Camakaris, & Danks, 1980), implying an underlying mechanism for development of IJP. Documentation of LO activity in cultured fibroblasts from these subjects and appropriate controls, while beyond the scope of this clinical investigation, would be a useful experimental approach to confirm this hypothesis.

We also surveyed the medical literature for prior reports of IJP in all pediatric subjects. We identified 85 total patients, and reviewed the distribution of this abnormality by gender, sidedness and underlying etiology. As noted, the literature review identified 6/85 examples of IJP in Menkes disease subjects. Combined with the present results, Menkes disease accounted for about 16% (15/94) of all reported pediatric patients with IJP. The cross-sectional IJ measurements in our Menkes subjects without phlebectasia were comparable to those determined previously in healthy children (Eksioglu, Tasci Yildiz, & Senel, 2014; Jeon et al., 2002).

Crying or the Valsalva maneuver can have a significant effect on IJ size both in healthy infants/children and those with phlebectasia. Eksioglu et al. (2013) determined a diagnostic cutoff for IJP of 2.2 cm^2

TABLE 4 Comparison of literature versus case studies presented in this article

Case studies from literature review (*N* = 85)			Menkes case studies in this article (*N* = 9)	
	N	%[a]	*N*	%
Age of patient at diagnosis				
<1 year	7	8%	0	0%
1–5 years	30	35%	9	100%
6–10 years	37	44%	0	0%
>10 years	11	13%	0	0%
Age of patient at reported first symptom				
<1 year	12	14%	1	11%
1–5 years	41	48%	8	89%
6–10 years	26	31%	0	0%
>10 years	6	7%	0	0%
Sex				
Female	27	32%	1	11%
Male	58	68%	8	89%
Side				
Right	64	75%	5	56%
Left	13	15%	0	0%
Bilateral	8	9%	4	44%
Causes				
No known/previously healthy	20	24%	0	0%
Other congenital vascular neck abnormalities[b]	7	8%	0	0%
Menkes disease	6	7%	9	100%
Family history of phlebectasia	2	2%	0	0%
No data reported	50	59%	0	0%
Clinical characteristics/comorbidities				
Gradual increase	18	21%	9	100%
Physical compression on adjacent structures[c]	9	11%	0	0%
Asthma	4	5%	0	0%
Other[d]	7	8%	0	0%
No data reported	52	61%	0	0%
Diagnostic evaluation				
Ultrasound	47	55%	9	100%
Radiography with contrast[e]	36	42%	0	0%
Surgical exploration	8	9%	0	0%
Magnetic resonance imaging or angiography	7	8%	0	0%
Other or not reported	3	4%	0	0%
Treatment				
Conservative	41	48%	9	100%
Surgical[f]	37	44%	0	0%
Not reported	2	2%	0	0%
Outcome				
Not reported[g]	37	44%	0	0%
Asymptomatic as of < or = 1 year follow up	23	27%	0	0%
Asymptomatic as of >1–5 year follow up	18	21%	4	44%
Asymptomatic as of >5 year follow up	3	4%	3	33%

(Continues)

TABLE 4 (Continued)

Case studies from literature review (*N* = 85)			Menkes case studies in this article (*N* = 9)	
	N	%[a]	*N*	%
Respiratory distress/failure in a Menkes disease patient, unrelated to phlebectasia	2	2%	2	22%
Venous thrombosis in Menkes disease patient	1	1%	0	0%
Died during surgery due to complications (1928)	1	1%	0	0%

[a]Percentages may not add to 100 due to rounding or multiple characteristics per patient.
[b]Included terms: bilateral asymmetric phlebectasia, partial or complete duplication of IJ vein, intracranial extension of phlebectasia, neck varices, external jugular aneurysm, and concurrent external jugular dilation.
[c]Included terms related to nerve, trachea, and vascular compression: dysphagia, dyspnea, vocal changes, paroxysmal cough, Horner's syndrome, and cyanosis.
[d]Included terms: Hx of croup, prematurity, fever/weight loss, tenderness, lymphoreticular hyperplasia, thrombus in the setting of no change during Valsalva, inguinal hernia, enlarged tonsils and adenoids, euthyroid goiter, neck abscess.
[e]Included terms: includes CT, phlebography, venography, direct injection of contrast, aortic arch studies, cinefluorography, digital subtraction vertebral angiogram (DSVA).
[f]Including patients with eventual surgical treatment after initial conservative approach.
[g]Included terms: well at time of discharge or time frame was not specific or quantified.

CSA during Valsalva. In this study, we did not intentionally elicit crying or the Valsalva maneuver, and our measurements reflect a range of patient activity and affect. Therefore, the number of patients whose IJ CSA exceeded the 2.2 cm^2 cutoff may represent an underestimate. Five of the nine subjects with phlebectasia in our data set had dramatically enlarged IJ veins, with visible neck bulges. Three of the four bilateral phlebectasias began as unilateral phlebectasias and then progressed to bilateral (Table 2, Figure 3).

In our literature review, reports of IJP histopathology (subjects who had surgical intervention) were found in 35 cases, and included abnormal connective tissue, endothelial structures, and muscle layers in conjunction with fibrosis. In two reports, normal IJ histology was found (Gordon, Rose, Kottmeier, & Levin, 1976; Sander, Elicevik, Unal, & Vural, 1999). We have not had an opportunity to evaluate IJ histopathology in Menkes disease subjects, however, previous studies of vasculopathy in this condition indicated vascular ectasia, presumably related to lysyl oxidase deficiency (Kaler et al., 1993).

IJP appears to be a relatively uncommon and clinically benign feature of classic Menkes disease, with no specific medical or surgical actionability. Abnormal neck masses due to IJP represent an underappreciated clinical feature of Menkes disease.

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CONFLICT OF INTEREST

The authors have no conflicts of interest related to this work.

AUTHOR CONTRIBUTIONS

Kristen E. Stevens and Julienne E. Price analyzed and collated the data, assembled the tables and figures, and drafted the article; Jamie Marko reviewed imaging results and contributed to the article. Stephen G. Kaler edited and contributed to the article, oversaw the entire project, and assumes responsibility for the accuracy and integrity of the work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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