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K.H. Nicolaides[a]
G. Azar[a]
R.J.M. Snijders[a]
C.M. Gosden[b]

[a] Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London;
[b] Medical Research Council, Human Genetics Unit, Edinburgh, UK

Fetal Nuchal Oedema: Associated Malformations and Chromosomal Defects

Abstract

During an 8-year period, oedema in the dorsal cervical region that produces a characteristic tremor on ballotement of the fetal head (nuchal oedema) was observed in 145 (7%) of the 2,086 fetuses that underwent karyotyping in our unit because of fetal malformations and/or growth retardation. Nuchal oedema was distinguished from nuchal cystic hygromata and from hydrops foetalis. In 132 (91%) of the cases with nuchal oedema, there were other fetal malformations, and 53 (37%) fetuses had chromosomal abnormalities, mainly trisomy 21 but also other trisomies, deletions or translocations, triploidy and Turner syndrome. Furthermore, the chromosomally normal fetuses with nuchal oedema had a very poor prognosis because, in many cases, there was an underlying skeletal dysplasia, a genetic syndrome or cardiac defect.

Key Words

Fetal nuchal oedema
Prenatal diagnosis
Ultrasonography
Fetal karyotype
Cordocentesis

Introduction

Infants with Turner syndrome and trisomy 21 often have excessive skin of the neck [1]. Antenatally, fetuses with Turner syndrome are recognized by the presence of dorsal cervical, septated, cystic hygromata [2]. Until now, the nuchal abnormality in fetuses with trisomy 21 has been defined as soft-tissue thickening >5 mm, seen in the suboccipitobregmatic view of the fetal head [3]. However, screening studies for the antenatal detection of trisomy 21 using this marker have produced conflicting results. Thus, Benacerraf et al. [3], in a series of 1,704 consecutive amniocenteses at 15–20 weeks' gestation in which there were 11 fetuses with trisomy 21, reported that 45% of the trisomic and 0.06% of the normal fetuses had nuchal thickness >5 mm [3]. Similarly, Lynch et al. [4], who retrospectively examined the sonograms of 9 pairs of discordant twins, found nuchal thickening >5 mm in 5 of the 9 fetuses with trisomy 21 but in none of the normal co-twins [4]. However, Perella et al. [5] retrospectively examined the sonograms of 14 fetuses with trisomy 21 and 128 normal controls and found nuchal thickening in only 21% of the trisomic fetuses and 9% of the normal ones [5].

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Dr. Kypros Nicolaides
Harris Birthright Research Centre
for Fetal Medicine
King's College School of Medicine
Denmark Hill, London SE5 8RX (UK)

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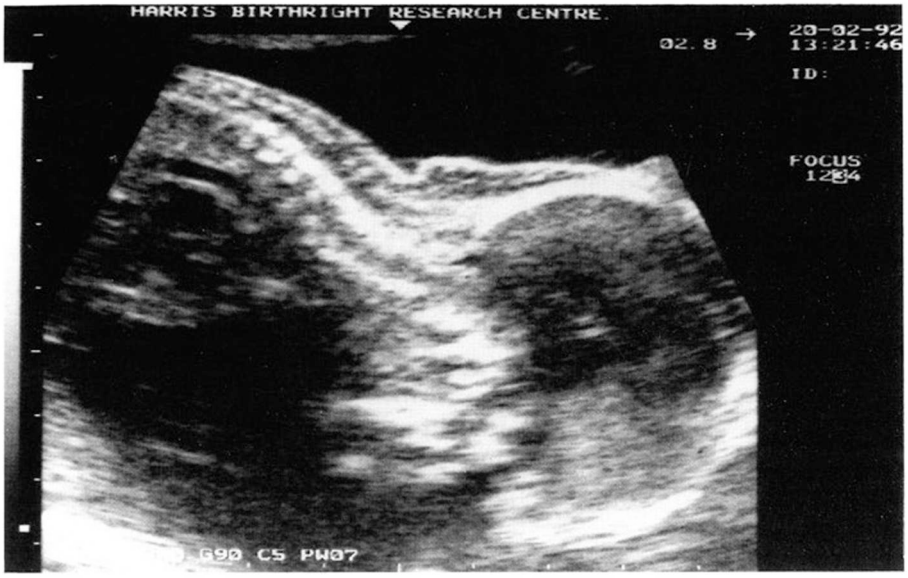

Fig. 1. Mid-sagittal view of the fetal neck demonstrating nuchal oedema.

One possible explanation for the conflicting results of these studies is that nuchal thickness, which is at least partly dependent on the degree of flexion of the fetal head and the angle of the plane of section of the fetal head [6], does not adequately describe the antenatal finding in trisomic fetuses. In our experience, these fetuses often have nuchal oedema, which produces a characteristic tremor on ballotement of the fetal head and is best seen in the mid-sagittal plane of the neck (fig. 1). This study examines the incidence of nuchal oedema in a high-risk population of 2,086 fetuses who were karyotyped because of ultrasonographically detected fetal malformations and/or growth retardation. The aim of the study is to determine the pattern of associated malformations and chromosomal abnormalities.

Patients and Methods

During an 8-year period (1983–1991), fetal karyotyping was performed in our unit in 2,086 patients who were referred because of ultrasonographically detected fetal malformations and/or growth retardation.

Nuchal oedema was considered to be present if, in the mid-sagittal plane of the neck, there was subcutaneous oedema that produced a characteristic tremor on ballotement of the fetal head. This was distinguished from nuchal cystic hygromata (a bilateral, septated and cystic structure, located in the occipitocervical region) and from hydrops foetalis, in which there was generalized oedema. The diagnosis of fetal malformations, such as exomphalos or spina bifida, was based on the ultrasonographic demonstration of well-described anatomical defects. The diagnosis of abnormal biometry was based on the finding of measurements above the 97.5th and below the 2.5th centiles of our reference ranges, derived from the cross-sectional study of 1,010 normal fetuses. Thus, in brachycephaly, the biparietal diameter (BPD) to occipitofrontal diameter ratio was $>$ 97.5th centile for gestation; in ventriculomegaly, the anterior and/or posterior cerebral ventricle to hemisphere diameter ratio was $>$ 97.5th centile; if the head circumference to femur length (GL) ratio was $>$ 97.5th centile, the fetus was considered to have a short femur, and if the ratio was $<$ 2.5th centile, microcephaly was diagnosed. Fetal growth retardation was considered to be present if the abdominal circumference was $<$ 5th centile. However, in those fetuses with malformations affecting the abdominal circumference, such as exomphalos, dilated bladder or ascites, growth retardation was diagnosed if both the head circumference and FL were $<$ 5th centiles of the respective reference ranges.

Table 1. Karyotype in 145 fetuses with nuchal oedema, 52 with cystic hygromata, 91 with generalized oedema, and in 1,798 without nuchal oedema, cystic hygromata or generalized oedema

Karyotype	Nuchal oedema	Cystic hygromata	Generalized oedema	Other
Normal	92	17	80	1,596
Abnormal	53	35	11	202
Trisomy 8 mosaic	–	–	–	1
Trisomy 9 mosaic	–	–	–	2
Trisomy 13	7	–	–	24
Trisomy 18	5	1	1	76
Trisomy 21	31	1	6	31
Trisomy 22	–	–	–	2
Trisomy marker	–	–	–	1
Trisomy 4q partial	1	–	–	–
Trisomy 11p partial	–	–	–	1
Trisomy 12p	–	–	–	1
Tetrasomy 12p	1	–	–	–
Translocation (1;1)	–	–	–	1
Translocation (4;15)	–	–	–	1
Translocation (11;12)	–	–	–	1
Translocation (17;19)	–	–	–	1
Deletion 2q–	–	–	1	2
Deletion 3p–	–	–	–	1
Deletion 4p–	1	–	–	4
Deletion 5q–	1	–	–	–
Deletion 5p–	–	–	–	1
Deletion 6p–	–	–	–	1
Deletion 7q–	–	–	–	1
Deletion 8q–	–	–	–	1
Deletion 8p–	–	–	–	1
Deletion 9p–	–	–	–	1
Deletion 13q–	–	–	1	–
Deletion 14q–	1	–	–	–
Deletion 21q–	–	–	–	1
Turner syndrome	3	33	–	2
47,XXY	–	–	1	2
47, XYY	–	–	–	2
Triploidy	2	–	1	39

Parents were counselled as to the possible association with chromosomal defects, and this study reports the findings in those who chose to have fetal karyotyping. Cordocentesis was performed as an out-patient procedure, and results from a lymphocyte culture [7] were given to referring obstetricians who undertook the further management of the pregnancies and subsequently provided details on outcome.

Results

In the total group of 2,086 fetuses, there were 145 with nuchal oedema, 52 with nuchal cystic hygromata and 91 with hydrops (generalized oedema without cystic hygromata). The incidence and pattern of chromosomal abnormalities in these three groups of fetuses are shown in table 1. In the total group of 2,086

fetuses, there were 202 with chromosomal abnormalities in the absence of nuchal oedema, cystic hygromata or hydrops foetalis.

In all 53 chromosomally abnormal fetuses with nuchal oedema, there were additional multisystem malformations, and the pattern of fetal defects was compatible with the type of the underlying chromosomal abnormality (tables 2, 3). For example, in trisomy 21, common additional defects included macroglos-

Table 2. Fetuses with nuchal oedema and trisomy 21. Data of individual cases including gestational age, ultrasonographic findings, karyotype, outcome and additional malformations

No.	GA	Additional malformations					Karyotype	Outcome
		IUGR	heart	kidneys	extremities	other		
1	23				SF		47,xy,+21	TOP
2	16				SF		47,xy,+21	TOP
3	27					ascites, pleural effusion	47,xx,+21	TOP
4	35					macroglossia	47,xx,+21	alive
5	33					macroglossia, duodenal atresia	47,xx,+21	alive
6	20					macroglossia, brachycephaly, CPC	47,xx,+21	TOP
7	22				clinodactyly	echogenic liver nodules	47,xx,+21	TOP
8	16				SF, clinodactyly		47,xy,+21	TOP
9	21				clinodactyly	duodenal atresia	47,xx,+21	TOP
10	20		(+)		SF, sandal gap		47,xx,+21	TOP
11	20			H1			47,xy,+21	TOP
12	19			H1	SF		47,xx,+21	alive
13	18			H1		brachycephaly	47,xx,+21	TOP
14	19			H1		brachycephaly	47,xy,+21	TOP
15	23	+		H1		brachycephaly	47,xx,+21	alive
16	19			H1	sandal gap		47,xx,+21	alive
17	23			H1	sandal gap	macroglossia	47,xx,+21	TOP
18	24			H1	sandal gap	macroglossia	47,xx,+21	TOP
19	20		(+)	H1		pleural effusion	47,xy,+21	TOP
20	22			H1	clinodactyly, sandal gap		47,xx,+21	TOP
21	37		(+)	H1	clinodactyly	macroglossia	47,xx,+21	TOP
22	18			H1			47,xy,+21	TOP
23	20			MK	SF		47,xy,+21	TOP
24	20		+				47,xy,+21	TOP
25	25		+		clinodactyly	ventriculomegaly	47,xx,+21	TOP
26	26		+	H1	SF, clinodactyly		47,xy,+21	TOP
27	23		+				47,xx,+21	NND
28	26		+				47,xx,+21	TOP
29	25	+	+		SF	duodenal atresia	47,xx,+21	TOP
30	18		+		SF, clinodactyly	pleural effusion	47,xy,+21	TOP
31	24	+			SF, clinodactyly		47,xy,+21	TOP

GA = Gestational age, weeks; IUGR = intra-uterine growth retardation; SF = short femur; TOP = termination of pregnancy; CPC = choroid plexus cysts; (+) = cardiac defects detected at post-mortem examination; H1 = mild hydronephrosis; MK = multicystic kidneys; NND = neonatal death.

sia, mild hydronephrosis, clinodactyly, sandal gap and cardiac abnormalities (table 2), whereas trisomies 13 and 18 were most commonly associated with brain defects, facial cleft and exomphalos (table 3). In 45 of the 53 cases, the parents elected to terminate the pregnancy. In the pregnancies that continued, there was 1 intra-uterine and 1 neonatal death, and 6 (11%) infants survived.

Table 3. Fetuses with nuchal oedema and chromosomal abnormalities other than trisomy 21: data on individual cases including gestational age, ultrasonographic findings, karyotype, outcome and additional abnormalities

No.	GA	Additional malformations						Karyotype	Outcome
		IUGR	heart	kidneys	brain	extremities	other		
1	17		(+)			OF, SF	SSS, MG, exomphalos	47,xy,+18	TOP
2	19				Holopr	RBF	BC	47,xx,+18	TOP
3	19	+			Ventr	RBF, OF, SF	MG	47,xy,+18	TOP
4	21		+		CPC			47,xy,+18	IUD
5	20		+	H1	Ventr, CPC	RBF	SSS, MG, exomphalos	47,xy,+18	TOP
6	22			H1				47,xy,+13	TOP
7	22			H1		RBF		47,xy,+13	TOP
8	20		+		Holopr	talipes, polydactyly	facial cleft, exomphalos	47,xy,+13	TOP
9	21	+	+	H1	PFC	talipes	facial cleft, MC, MG	47,xy,+13	TOP
10	21		+	H1		talipes, polydactyly	facial cleft, exomphalos, MG	47,xy,+13	TOP
11	19		+	H2	Holopr	SF	hypotelorism	47,xy,+13	TOP
12	22		+	H2	PFC	RBF, OF	facial cleft, exomphalos	47,xy,+(13, 14)	TOP
13	21	+				syndactyly, SF	molar placenta	69,xxy	TOP
14	23	+		MK		syndactyly	molar placenta, BC	69,xxx	TOP
15	23						BC	45x	alive
16	19		+			sandal gap, SF	pleural effusion	45,x	TOP
17	22		+	H1		SF		45,x	TOP
18	25	+						46,xy,4p-	TOP
19	23					talipes	diaphragmatic hernia, MG	46,xx,5q-	TOP
20	24		+	H1	CPC	SF		46,xy,14q-	TOP
21	18		+			SF	facial cleft	47,xy,+4q	TOP
22	19		+	H1	Ventr	RBF, OF, SF	diaphragmatic hernia	46,xy,iso (12p)	TOP

Abbreviations as defined in table 2.

OF = Overlapping fingers; SSS = strawberry-shaped skull; MG = micrognathia; Holopr = holoprosencephaly; RBF = rocker-bottom feet; BC = branchycephaly; Ventr = ventriculomegaly; IUD = intra-uterine death; PFC = posterior fossa cyst; MC = microcephaly; H2 = moderate hydronephrosis.

Table 4. Chromosomally normal fetuses with nuchal oedema and multiple defects including renal or cardiac abnormalities

No.	GA	Additional abnormalities						Out-come	Diagnosis
		IUGR	heart	renal	brain	extremities	other		
1	21		(+)				umbilical cyst	NND	aortic valve stenosis
2	23	+	+			syndactyly	anopthalmia, absent fibula	TOP	
3	19	+	+			SF		NND	Charge syndrome
4	17		+			SF		TOP	
5	27		+				ascites	TOP	
6	33	+	+					alive	
7	20	+	+			talipes		TOP	
8	21		+		Holopr	SF	facial cleft, kyphoscoliosis	TOP	
9	20		+		Inienc	RBF, SF		TOP	
10	20		+		PFC	SF, polydactyly	narrow chest, brachycephaly	TOP	Ellis-van Creveld syndrome
11	21		+	RA	Ventr		kyphoscoliosis	TOP	
12	22		+	H1				TOP	
13	17		+	H1		SF		alive	
14	29		+	H1		SF		IUD	
15	30		+	H2		SF, clinodactyly	pleural effusion	NND	Noonan syndrome
16	27	+		H1				IUD	placental insufficiency
17	24	+		H1				IUD	placental insufficiency
18	24	+		H1				IUD	placental insufficiency
19	21			H1			MG	TOP	
20	19			H1			exomphalos	TOP	
21	23			H1	Ventr			TOP	
22	21			H1	Ventr	talipes		TOP	
23	19			PI	Ventr			TOP	
24	21			H2	Ventr			TOP	urethral atresia
25	20			H2		talipes	flexed wrists	IUD	arthrogryposis
26	21			H2	BC	SF, talipes	narrow chest, flexed wrists	TOP	chondrodysplasia punctata
27	18			H1	BC	SF	MG, pleural effusion	NND	cardiomyopathy
28	22			H1		SF, clinodactyly		NND	imperforate anus
29	21			MK	CPC		kyphoscoliosis	TOP	anal + urethral atresia
30	20			H2		RBF		NND	
31	23			H2				alive	
32	21			H2				alive	
33	21			H2				IUD	developed hydrops
34	27			H2				TOP	
35	20			MK		SF		TOP	
36	21			MK				TOP	branchio-otorenal dysplasia
37	19			MK		SF, talipes	exomphalos	TOP	rectal agenesis
38	25	+		MK		clinodactyly		IUD	

Table 5. Chromosomally normal fetuses with nuchal oedema and multiple defects other than renal or cardiac abnormalities

No.	GA	Additional abnormalities				Out-come	Diagnosis
		IUGR	brain	extremities	other		
1	27	+				alive	placental insufficiency
2	28	+				alive	placental insufficiency
3	23	+				IUD	placental insufficiency
4	20	+				IUD	placental insufficiency
5	30	+		OF, talipes		IUD	
6	22	+		SF		IUD	placental insufficiency
7	24	+			ruptured membranes	IUD	
8	23	+			MG (cleft palate)	NND	
9	33			clinodactyly	macroglossia	alive	
10	21				ascites	NND	Pierre-Robin syndrome
11	21				ascites	TOP	
12	20				pleural effusion	NND	myocarditis
13	38			OF	diaphragmatic hernia	alive	
14	22				diaphragmatic hernia	TOP	
15	18		CPC	talipes	kyphoscoliosis	TOP	
16	21		CPC			alive	
17	21		PFC	OF, talipes		TOP	
18	34		Ventr			alive	
19	30	+	Ventr	sandal gap	MC	NND	
20	24	+	Holopr	OF	facial cleft, MC	TOP	
21	22		Ventr		facial cleft	TOP	
22	33	+		SF	facial cleft (duodenal atresia)	NND	
23	19		Ventr	SF, talipes	narrow chest, CSS	TOP	asphyxiating thoracic dystrophy
24	20			SF	narrow chest, pleural effusion	TOP	asphyxiating thoracic dystrophy
25	18			OF,SF, talipes	SSS	TOP	

Abbreviations as described in tables 2–4.
CSS = Clover-shaped skull.

(Footnote to table 4)

Abbreviations as defined in tables 2, 3.
Inienc = Iniencephaly; RA = renal agenesis; PI = infantile polycystic kidneys.

In the group of 92 chromosomally normal fetuses with nuchal oedema, additional defects and/or growth retardation were detected in 79 (86%) of the cases. In all 13 fetuses with isolated nuchal oedema and in the 16 where the additional defects were mild hydronephrosis (n = 12) and/or digital abnormalities (n = 7), the infants survived; in only 2 of the cases, the nuchal oedema persisted in the neonatal period. In contrast, in the 63 cases with

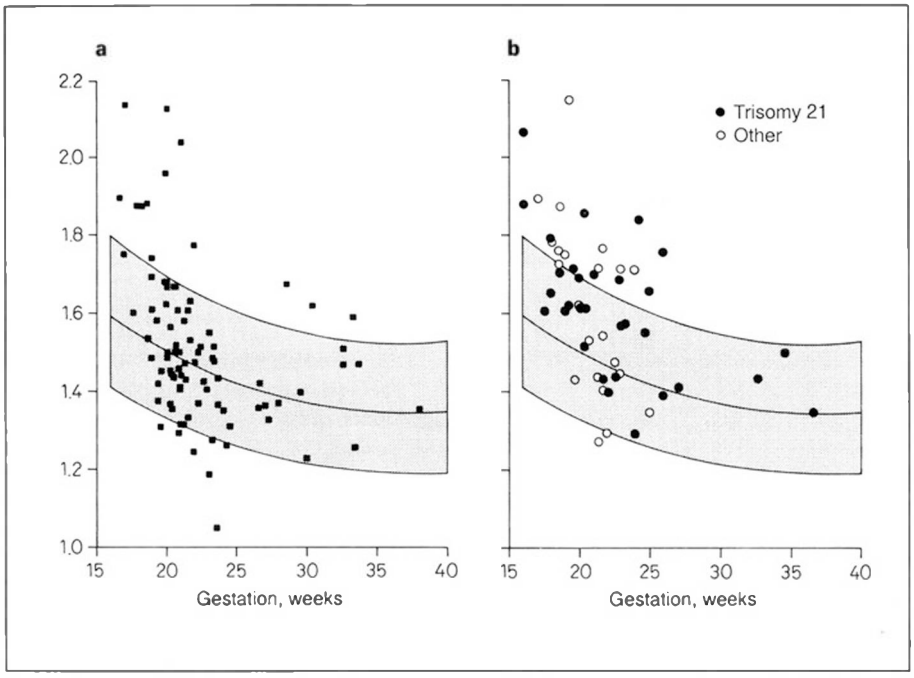

Fig. 2. BPD:FL ratio in chromosomally normal (**a**) and abnormal (**b**) fetuses with nuchal oedema plotted on the reference range (mean, 95th and 5th centiles) for gestation.

growth retardation and/or other system abnormalities (tables 4, 5), survival was only 16% (10 cases). There were 30 terminations of pregnancy, 12 intra-uterine deaths and 11 neonatal deaths. The commonest defects in these 63 fetuses were craniospinal, cardiac, renal and skeletal. In a substantial proportion of cases, the features were compatible with well-described syndromes, such as Ellis-van Creveld, Noonan, Charge and Pierre-Robin syndromes, asphyxiating thoracic dystrophy, arthrogryposis, chondrodysplasia punctata and branchio-otorenal dysplasia. Furthermore, in growth-retarded fetuses with no other defects, Doppler studies of the uteroplacental and fetal circulations were suggestive of uteroplacental insufficiency.

The mean gestation at referral of the fetuses with nuchal oedema was 22 weeks (range 16–38) and there was no significant difference between the chromosomally normal and abnormal groups ($t = -0.66$). In contrast, the mean maternal age of the chromosomally abnormal group (32 years, range 20–44) was significantly higher ($t = 3.55$, SEM = 0.92, $p < 0.001$) than that of the chromosomally normal group (28 years, range 18–38).

In both the chromosomally normal and abnormal groups with nuchal oedema, the mean BPD and FL were significantly lower than the appropriate, normal mean values for gestation. However, in the chromosomally abnormal fetuses, the mean FL was significantly lower and the mean BPD/FL higher than respective means of the chromosomally normal group (fig. 2).

Discussion

The findings of this study indicate that (a) nuchal oedema has a high association with multisystem fetal malformations and chromosomal abnormalities, primarily trisomy 21, but also trisomies 13 and 18, triploidy, deletions and translocations; (b) the pattern of associated chromosomal abnormalities, trisomes rather than Turner syndrome, demonstrate that nuchal oedema is a distinct entity from nuchal cystic hygromata, but it may constitute one end of the spectrum of hydrops foetalis, and (c) chromosomally normal fetuses with nuchal oedema have a poor prognosis, because in many cases there is an underlying skeletal dysplasia, a genetic syndrome or cardiac defect.

Nuchal oedema, like nuchal cystic hygromata or hydrops foetalis, is a 'gestalt' marker, rather than a measurable feature, of chromosomal abnormalities, and it can be easily recognized in the mid-sagittal view of the fetal neck. The finding of nuchal oedema should prompt the ultrasonographer to undertake a diligent search for the presence of other major and minor defects associated with chromosomal abnormalities, and it is a strong indication for fetal karyotyping. Although the mean BPD:FL ratio in chromosomally abnormal fetuses with nuchal oedema is significantly higher than that of the chromosomally normal fetuses, the large overlap in values between the two groups precludes a clinically useful role for this index.

Nuchal cystic hygromata are thought to be the consequence of an abnormal development of the thoracic duct [8]. The underlying mechanisms for nuchal oedema are likely to be diverse, and the condition should be considered as an early manifestation or mild degree of hydrops foetalis. Therefore, nuchal oedema, like hydrops foetalis, may be a non-specific finding in a wide variety of fetal and maternal disorders, including fetal cardiovascular and other malformations, genetic diseases, congenital infection, metabolic or haematological abnormalities. In this respect, antenatal investigations should include detailed ultrasonography and echocardiography, fetal karyotyping and infection screening. Furthermore, the parents should be counselled that even if the fetal karyotype is normal, the prognosis could be poor.

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