Original Research Article

Evaluate of leprosy affected nerves using high resolution ultrasonography and color doppler

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Abstract

Introduction: Leprosy is the most common treatable peripheral nerve disorder worldwide with periods of acute neuritis leading to functional impairment of limbs, ulcer formation and stigmatizing deformities. Since the hallmarks of leprosy are nerve enlargement and inflammation, we used high-resolution sonography and color Doppler imaging to demonstrate nerve enlargement and inflammation. **Aims:** To evaluate leprosy affected nerves using High Resolution Ultrasonography and Color Doppler and possibility of prediction of Reactions using High Resolution Ultrasonography and Color Doppler. **Materials and methods**: This is a prospective study for a period of 2 years includes 30 healthy controls and 30 patients of both genders with aged between 17 to 58 years (mean 33+ /-10) with cross- sectional areas (CSAs) of the MN, UN, lateral popliteal (LP) and PT nerves. 30 leprosy patients, diagnosed as per Ridley- Jopling classification, who were in different stages of therapy with WHO multi-drug therapy, were included for evaluation. **Results:** 1 patient had TT, 12 patients had borderline tuberculoid, 1 had Borderline borderline, 6 patients had Border line lepromatous and 4 lepromatous leprosy, 6 Pure Neuritic leprosy. 4 had type 1 reaction and 2 patients had type 2 reactions, which was associated with neuritis. Skin smears were positive in 12 patients. Clinical thickening, ranging from grade 1 to 3, was observed in 193 nerves of the 240 examined nerves (72%). Significant correlation was observed between clinical parameters of grade of thickening, sensory loss and muscle weakness and US abnormalities of cross- sectional areas, echotexture, endoneural flow (p, 0.001). Increased **color doppler** was observed in multiple nerves in 3 out of 4 patients undergoing type 1 reaction, which is considered to be localized to the dermal lesions and the neighbouring nerves. In patients with a type 2 reaction, blood flow signals in multiple nerves was seen in 2 out of 2 patients. **Conclusion:** The clinical and ultrasonographic changes of leprosy affected nerves is well correlated so help us to predict the possible occurrence of the reactions in thickened nerves on periodic examination.

Keywords: High-resolution sonography, Color Doppler, Leprosy.

Introduction

Leprosy is the most common treatable peripheral nerve disorder worldwide. Leprosy is caused by a chronic granulomatous immune response to infection of the skin and nerves with Mycobacterium leprae, which resides in macrophages and Schwann cells and is the only bacterium known to affect myelination and cause peripheral neuropathy. Nerve damage, affecting mainly the ulnar (UN), median (MN), and posterior tibial (PT) nerves, results in nerve enlargement leading to deformities[1].

Leprosy presents as a clinico-pathological spectrum ranging from the localized paucibacillary tuberculoid form with anaesthetic hypopigmented skin patch (TT) to the generalized multi- bacillary, lepromatous leprosy.

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Between these poles are unstable forms of borderline tuberculoid, borderline borderline and borderline lepromatous leprosy. These are prone to episodic exacerbations (reactions) in 15–50% of patients during the course of the disease and after the completion of multidrug therapy. These states include type 1 (reversal reaction), where only the skin patch shows inflammation with tenderness in the associated nerve, and type 2 [Erythema Nodosum Leprosum (ENL)] reaction, manifesting with systemic symptoms of fever, erythematous nodules and joint pains. Though some nerve involvement may be seen in all types of leprosy, leprosy reactions lead to severe morbidity and acute neuritis requiring immediate treatment. Efforts to diagnose early (or subclinical) neuritis could ameliorate the nerve damage leading to functional impairment of limbs, ulcer formation and stigmatizing deformities. Hence, the most important goal in the management of leprosy is the prevention of disability via early detection of nerve impairment[1,2].

Careful clinical testing is useful, but can only detect the presence of neuropathy. However if neuropathy is found, there already is a substantial amount of nerve damage. Nerve conduction studies or warm perception testing may improve early detection strategies, but these are usually not available in leprosy centers. Since the hallmarks of leprosy are nerve enlargement and inflammation, we decided to use high-resolution sonography to demonstrate nerve enlargement (even

sub clinically) and inflammation. Inflammation can be detected by increased blood flow signals in the epi- and endoneurium of the involved nerves in leprosy patients[1].

Leprosy is essentially a disease of the peripheral nervous system despite prominent involvement of the skin and certain other tissues. Among known peripheral neuropathies, leprosy is one of the most frequent and disabling diseases, because of combined impairment of autonomic, sensory and motor fibres and the social stigma attached to the disease. Most of this disability is preventable through early detection of leprosy and prompt treatment with multidrug therapy (MDT). Besides MDT, the main method of prevention of nerve function impairment (NFI) and disability is regular nerve function assessment (NFA) and timely steroid treatment when new neural impairment occurs[2].

Around 10% of the 300,000 or so new cases detected every year have clinical signs of neuropathy at diagnosis. However, there is evidence that extensive nerve damage has already taken place before clinical signs of leprosy are evident. A large proportion *(*up to 86% of all new NFI events may be 'silent' (no symptoms of pain or clinical signs other than those evident on clinical testing). Many researchers believe that all leprosy patients have involvement of the peripheral nervous system. Even after the start of MDT, new episodes of NFI from immunological 'reactions' are common, in particular in multibacillary (MB) patients with long-standing NFI at registration[3,4]. We aim to evaluate the finer details of leprosy affected nerves using High Resolution Ultrasonography and Color Doppler and possibility of prediction of Reactions using High Resolution Ultrasonography and Color Doppler

Materials and methods

This is a prospective study from December 2011 to August 2013 conducted at Department of DVL, OSMANIA MEDICAL COLLEGE , Hyderabad. Study includes 30 healthy controls and 30 patients as follows.

Thirty healthy volunteers 15 of each gender, aged between 17 to 58 years (mean 33+ /-10) without any evidence of diabetes, hypothyroidism, HIV and trauma-related peripheral nerve disease were included in the study to obtain normal values of the cross-sectional areas (CSAs) of the MN, UN, lateral popliteal (LP) and PT nerves. 30 leprosy patients, diagnosed as per Ridley- Jopling classification[5], who were in different stages of therapy with WHO multi-drug therapy, were included for evaluation. All the subjects were included in the study after obtaining an informed written consent.

Clinical evaluation/grading of nerves

All the volunteers and patients were examined by two clinicians trained in leprosy to assess bilaterally the UN, MN, LP and PT nerves. All the nerves were examined for their motor and sensory functions as follows.

MN: We evaluated pin-prick sensation in the distribution of the median nerve using monofilaments and assessment of motor function of abductor pollicis brevis (APB).

LP: The strength of the extensor hallucis longus and M. tibial anterior was tested using the Medical Research Council (MRC) rating scale

PT: Current symptoms of lesion of the posterior tibial nerve were tested by pin-prick sensation at the heel and sole of the foot using monofilaments and the muscle strength of the toe and foot flexors.

UN, MN,CPN and PTN were clinically graded after palpation as follows.

Grade 0 was defined as a nerve not thicker than the contralateral nerve and with normal sensation;

Grade 1 occurred when the affected nerve was thicker than the contralateral nerve;

Grade 2 was a thickening of the affected nerve which felt rope-like;

Grade 3 was a thickened nerve which felt beaded or nodular.

Skin smears were taken from three sites for presence of acid-fast bacilli and to assess the Bacillary Index (BI). Skin biopsy was performed to confirm the clinical diagnosis.

Ultrasonography (US) and color doppler (CD)

All peripheral nerves were imaged by an independent radiographer blinded to the clinical diagnosis using US (Voluson -730 Expert, GE medical, USA) with broadband frequency of 10–14 MHz; CD frequency of 6–13 MHz and linear array transducer. Bilaterally, the MN at the wrist and forearm, the UN at the elbow and proximal to the medial epicondyle, LP at the fibula head and PT nerves at the ankle and proximal to the medial malleolus were examined and the length of abnormality of the nerve was determined by the presence of abnormal size and echo reflectivity of the nerves. All nerves were measured on transverse sections at a point where the nerve thickness was maximum in the visualized segment of the nerve. On transverse scans, the cross- sectional area of the nerve was determined from that area by one measurement within the hyperechoic rim surrounding the nerve. The echo reflectivity of the nerves assessed on imaging was arbitrarily graded as follows:

mild = some hypo-reflectivity,

moderate = obvious hypo-reflectivity; and

severe = absence of any fascicular pattern.

Color Doppler (CD) settings were chosen to optimize identification of weak signals from vessels with slow velocity. Pulse repetition frequency was set of 1 KHZ and Doppler gain was adjusted to the maximum level that thus not produce clutter. Band filter was set at 50 Hz. The presence of blood flow signals in the perineural plexus or interfascicular vessels indicated hypervascularity of the nerve during CD imaging.

Statistical analysis

Statistical analysis was performed using SPSS software version 11/ graph pad prism version 4. For comparison of group differences, the one-way nonparametric analysis of variance (Kruskal- Wallis test) or the Wilcoxon- Mann-Whitney test were used. For the comparison of proportions the x2 test was used. Probability (p) values less than 0.05 were considered significant.

Results

A Transverse scan of medial nerve from a healthy subject as denoted by dotted ellipse (CSA = 4.5 mm^2) showing hypoechoic fascicles separated by hyper- echoic areas in a 'honeycomb' like pattern with absence of blood flow signals;

B longitudinal ultrasonogram of ulnar nerve from a healthy subject (arrows) with hyperechogenic bands in a linear pattern appearing as bundles of straw

Table 1: Cross sectional area (mm2) of major peripheral nerve trunks of upper and lower limbs of healthy subjects

Subjects	Ulnar nerves	Median nerves	Lateral popliteal nerves	Posterior tibial nerves
Healthy subjects(30)				
Mean± SD	8.3±3.7	6.3±2.2	6±3	6.4±3.2
Median	8	6	6	6
Range	3.3-16.6	3.1-11.9	3-11.9	2.2-15.4
Leprosy patients(30)				
Mean± SD	19.77+/-16.511	14.23+/-8.241	12.63+/-4.906	12.82+/-6.440

Median	17.5	12	12	11
Range	5-125	3-52	5-28	4-45
p-value	0.0001	0.0001	0.0001	0.0001

On palpation, all the nerve trunks were of normal size (grade 0) and not tender. On US, the peripheral nerves appeared as round to oval with occasional internal punctuate echoes giving a 'honey comb pattern' in transverse scans , and as hypoechoic tubular structures with parallel linear internal echoes suggestive of 'bundles of straw' in longitudinal scans. The epi- and perineurium were uniformly hyperechoic with an absence of endo and epineural blood flow signals on CD imaging. The mean CSA for all 4 nerves showed no age or gender related differences. The ulnar nerve showed the highest mean CSA as compared to the other nerves

Table- 2: Distribution of the cases with respect to clinical type

Clinical type	Number of patients
Tuberculoid Leprosy	01
Borderline Tuberculoid	12
Borderline borderline	01
Borderline Lepromatous	06
Lepromatous Leprosy	04
Pure Neuritic leprosy	06
Total	30

1 patient had TT, 12 patients had borderline tuberculoid, 1 had Borderline borderline, 6 patients had Border line lepromatous and 4 lepromatous leprosy, 6 Pure Neuritic leprosy.

Table-3: Patient characteristics

Age (years)	Number of Cases
10- 20	02(6.6%)
21- 30	08(26.7%)
31- 40	11(36.7%)
41- 50	09(30%)
>50	00(00%)
Total	30
Gender	
Males	20(66.7%)
Females	10(33.7%)
Occupation	
Labourers	06
Agricultural workers	06
Students	06
House wives	06
Others	06
Socioeconomic status	
Low	17(56.6%)
Middle	12(40%)
High	01(3.4%)
Duration	
0-3 months	06
4-6 months	08
7-9 months	04
10-12 months	05
13-15 months	01
16-18 months	01
19-21 months	00
22-24 months	04
>24 months	01

4 had type 1 reaction and 2 patients had type 2 reactions, which was associated with neuritis. Skin smears were positive in 12 patients.

Table-4: Distribution of the cases with respect to duration treatment

With respect to duration of the reaction	Number of patients
0-1 month	03
2-3 months	02
>4 months	01
Total	06

With respect to duration of the MDT treatment	
0-1 month	18
2-3 months	04
4-5 months	05
6-7 months	03
Total	30
Deformity	
No deformity	13
Nasal depression	01
Claw hand	13
Foot drop	02
Claw foot	00
Resorption of digits	01
Total	30

Clinical thickening, ranging from grade 1 to 3, was observed in 193 nerves of the 240 examined nerves (72%).

Table-5: Clinical and sonographic findings of major peripheral nerves of upper and lower limbs in 30 leprosy patients

Characteristics	Ulnar nerves(60)	Median nerves(60)	Common popliteal nerves(60)	Posterior tibial nerves(60)	All nerves
Clinical involvement					
Thickening(238)					238
Grade 0	03(5%)	28(47%)	7(11.7%)	7(11.2%)	45(19%)
Grade 1	23(38%)	31(52%)	43(72%)	46(77%)	143(60%)
Grade 2	29(48%)	01(2%)	10(17%)	5(8.3%)	45(19%)
Grade 3	5(8.3%)	00	00	00	5(2.1%)
Sensory loss(240)	13(21.6%)	15(25%)	29(48.3%)	33(55%)	90(37.5%)
Motor weakness(240)	18(30%)	6(10%)	3(5%)	1(1.6%)	28(11.6)
Both motor and sensory loss(240)	4(6.6%)	3(5%)	3(5%)	1(1.6%)	
Normal	3(18%)	28(46.7%)	7(11.6%)	7(11.6%)	
Sonographic findings					
Echo reflectivity					
Normal	34	51	51	57	
Mild	18	6	9	2	
Moderate	4	3	0	1	
Severe reduced	4	0	0	0	
CSA enlargement	43(71.6%)	49(81.6%)	46(76.6%)	48(80%)	
Increased CD	10(16.7%)	2(3.3%)	4(6.6%)	1(1.6%)	

2 patients who did not have nerve enlargements did not have a type 1 or type 2 reaction or signs of neuritis. Very enlarged nerves with a CSA. 50 mm^2 were observed in four nerves (3 UN and 1MN) and all these patients had a type 1 reaction. When the sonographic findings and the clinical characteristics were analysed, significant differences were observed in the mean CSA for clinical grades 0 versus grades 1 ($p = 0.02$), 2 ($p = 0.002$) and 3 ($p = 0.0003$).

In the 45 nerves for which clinical thickening was not observed (3 UN, 26 MN, 5 CPN and 5 PTN) by palpation (grade 0), the CSA was above the upper limit of normal in 3 0 nerves (1 UN, 22MN, 4 CPN, 3 PTN). On the contrary, 21 of the 201 clinically thickened nerves (4 UN, 6MN, 5 LP, and 6 PT) did not show sonographic enlargement.

Clinical grade 2 and higher nerve enlargements were only found for UN and in few LP but not in MN and PT nerves. Out of 3 clinically not enlarged UNs, 2 showed sonographic enlargement, 1nerve did not show it. Out of 26 clinically not enlarged nerves, 19 showed sonographic enlargement, 7 nerves did not show it.

Out of 5 clinically not enlarged CPNs, 4 showed sonographic enlargement, 1 did not show it.Out of 5 clinically palpable PTNs, 4 showed sonographic enlargement, 1 did not show it.

CD flow signals were observed in 1 of the 45 clinically non-thickened nerves (2%) it was in MN. Blood flow signals were observed in 7 of 143 grade 1- thickened nerves (4.9%), 7 of 45 grade 2- thickened nerves (15%) and 2 of 5 grade 3- thickened nerves (40%). This indicated that the more the nerve was clinically enlarged, the more often CD flow signals were present (p, 0.0001)

In the 30 nerves of 12 patients with sensory loss , the nerve supplying the area of sensory loss was sonographically enlarged in 23 nerves (77%). Significant correlation was observed between clinical parameters of grade of thickening, sensory loss and muscle weakness and US abnormalities of CSA, echotexture, endoneural flow (p, 0.001).

Sonographic characteristics

Echotexture and CD flow: Of the 240 nerves examined in the leprosy patients, 193(80%) of the nerves showed normal echo patterns. In the remainder, moderate or severe reduced echo reflectivity, indicative of partial to total loss of fascicles structure. Mild, moderate and severe echo reflectivity changes were observed respectively in 35, 8% and 4% of the nerves examined.

The longest lengths were measured in the UN and MN. UN was found to be most enlarged 4–6 cm above the sulcus and with MN approximately 4 cm proximal to carpal tunnel inlet. There was a highly significant correlation between CSA and echotexture grading ($p = 0.0001$). Endo or perineural flow suggestive of increased neural vascularity by CD imaging was observed in 17 out of 238 examined nerves (26%). Neural vascularity was observed more frequently in upper limb nerves with UN being most affected (58%) followed by the median nerve (25%).

Bilateral involvement was also seen more in the UN and the MN. In the lower limb nerves, CPN (6.6%) showed a higher percentage of neural vascularity compared to PT nerves (1%). 9 nerves with neural vascularity were from the 6 patients who had associated leprosy reactions. . Of the 9 nerves with increased flow, 6 were from 4 patients with type 1 reaction and 3 were from the 2 patients with a type 2 reaction.

In 5 out of the 8 patients with associated leprosy reactions, neural vascularity on CD imaging were seen in the nerve trunk on the side of the inflammed skin lesions and in contralateral and distant nerve trunks, suggesting more extensive involvement of nerves during reactions of leprosy compared to clinical skin involvement. Increased CD was observed in multiple nerves in 3 out of 4 patients undergoing type 1 reaction, which is considered to be localized to the dermal lesions and the neighbouring nerves. In patients with a type 2 reaction, blood flow signals in multiple nerves was seen in 2 out of 2 patients.

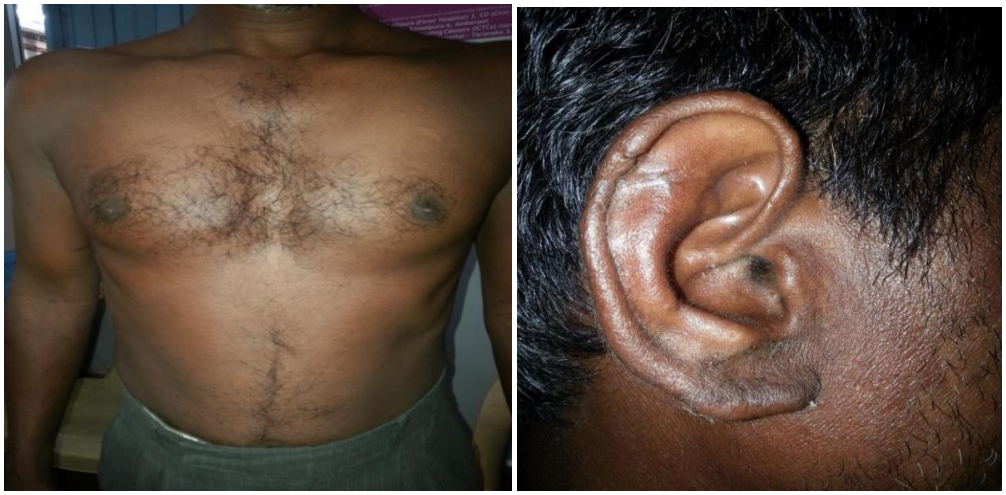

Fig 1: Photos in cases

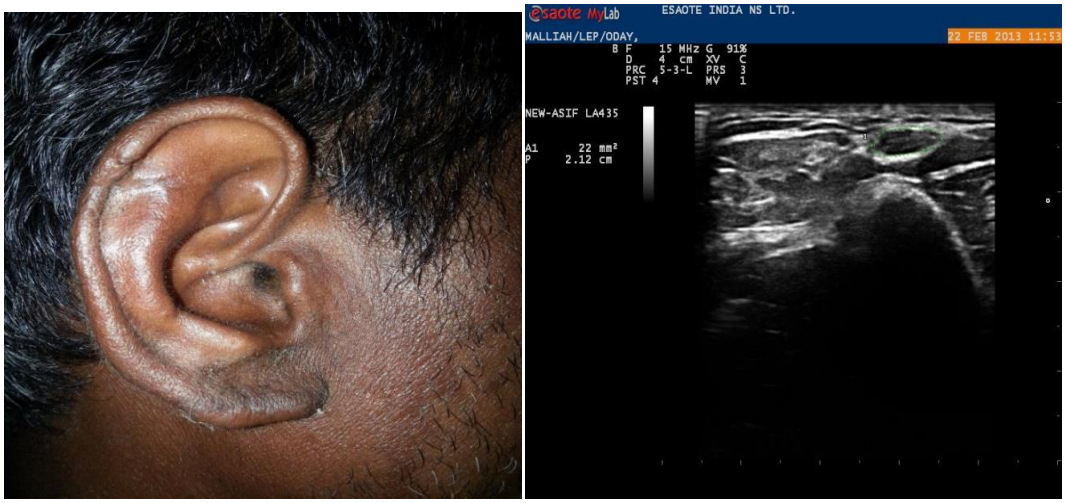

Fig. 2: Case of borderline tuberculoid

Discussion

Elimination of leprosy was declared by WHO in INDIA. But Leprosy is still there, presenting with most Stigmatizing deformities, prime structure affected being Nerve leading to Neuritis. It becomes essential to find and study an investigating tool to detect early nerve damage to prevent it and thereby Neuritis and deformities. High Resolution Ultra Sonography and Color Doppler is one of them. Exact quantification of extent of thickness of affected nerves using CSA (mm2), the length of involvement of nerves, the internal mileau of nerves like Echotexture represented by fascicular arrangement and the vasculature of nerve are the parameters studied using the diagnostic tools.

The analysis of the above parameters of normal and affected nerves in one study demonstrates the usefulness of US in detecting nerve damage in leprosy. Our findings may have clinical and therapeutical consequences. Peripheral nerves are often enlarged in leprosy, and these are more accurately assessed by US than by clinical palpation. UN is the most commonly involved nerve.

The studies have been reviewed. High-Resolution Sonography was used to Detect Nerve Damage in Leprosy by Suman Jain et al study[6]. US and MR imaging in peripheral nerves in leprosy. By Martinoli et al has found that leprosy can produce a wide spectrum of nerve abnormalities in USG and MR due to inflammatory and degenerative changes, acute reaction states and entrapment syndromes. Our study is in concordance with the above study in detected nerve damage on leprosy. Morphological changes of the epineurium in leprosy. A new finding detected using HRUS by Leo H. Vissar et al[6].

In Echotexture of peripheral nerves correlation between USG and Histopathological findings by criteria to differentiate tendons by Enzo

Silvestri MD et al[7]. Use of HRUS as an additional tool in the diagnosis of primary neurotic leprosy by Suman jain et al[6]. Diagnostic and control changes for world-wide disease by Isabela Maria Bernardes Goulart et al[8]. Biology of nerve injury in leprosy by David M Scolard USA 2008[9]. Peripheral nerves of the extremities imaging with US. HRUS of peripheral nervous system in review of literature by R Bekman and L H Vissar et al[10].

Table-6: Comparison of studies on Echo Reflectivity/ Fascicular Pattern

DEGREE of Severity	Jain et al[6]				Present Study			
	No of Nerves in Cases	%	No of Nerves in controls	%	No of Nerves in Cases	%	No of Nerves in controls	%
MILD	25	16.4	0	0	35	14.5	0	0
MODERATE	45	29.7	0	0	8	3	0	0
SEVERE	6	3.9	0	0	4	1.6	0	0

In Jain et al study, moderate>mild>severe was observed. While in our study, mild > moderate > severe disturbance in fascicular pattern was noticed.

Table-7: Comparison of studies on Flow on Color Doppler

NERVES	Jain et al[6]		Present Study	
	No of Nerves	%	No of Nerves	%
UN	23	58.9	10	16.7
MN	10	25	2	3.3
CPN	4	10.5	4	6.6
PTN	2	5.5	1	1.6
TOTAL NERVES	39	25.6	17	7.08

Increased flow on color Doppler was observed in 25.6% nerves in Jain et al study, while in 7.08% nerves in our study. This difference is probably because of only 6 cases of reactions recorded in our study.
Leo H Visser et al study states and proves there is significant epineural thickening in leprosy effected nerves. In our study also, we found there was significant epineural thickening[10].

Conclusion

High Resolution ultrasonography and Color Doppler are superior investigative modalities in detection of early nerve damage in leprosy affected nerves in terms of measurement of CSA, Length of affected nerve, Fasicular pattern, Vasculature of nerve, Epineural thickening which are not appreciated by clinical examination. The clinical and ultrasonographic changes of leprosy affected nerves can be very well correlated. These modalities may help us to predict the possible occurrence of the reactions in thickened nerves on periodic examination.

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