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Periodic Leg Movements in Sleep and Restless Legs Syndrome: Considerations in Geriatrics

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Keywords

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Introduction

Both periodic leg movements in sleep (PLMS) and restless legs syndrome (RLS) are common conditions in elderly populations. In this paper, we review relevant knowledge regarding their prevalence and associated conditions, discuss technical considerations related to the polysomnographic characterization of PLMS in relation to age, evaluate possible manifestations of these conditions in dementia and offer some brief perspectives on treatment considerations. Although PLMS does not approach 100% sensitivity and 100% specificity as a marker of RLS (specificity lags because many patients without RLS still demonstrate PLMS), both conditions show a high prevalence in the older adult. PLMS and RLS are defined from different data sources (polysomnographic criteria for PLMS, clinical criteria for RLS), though their considerable overlap has led many researchers[1] to argue that PLMS represents the single best objective marker of a condition (i.e., RLS) that may be complex and variegated, and may have somewhat unique characterization in geriatrics[2].

PLMS: Prevalence and Associated Factors

PLMS are stereotypic, repetitive, non-epileptiform movements of the lower limbs typically occurring during NREM sleep but occasionally occurring in REM sleep and in some situations discernible in the waking state as well. PLMS typically consist of dorsiflexion of the anterior tibialis muscle, although movements may involve the hip or be confined to the great toe (extensor hallucis longus). PLMS represent a physiologic finding made with polysomnography or ankle-mounted actigraphy. The best single-night estimate of PLMS prevalence is about 45% in an unselected geriatric population derived from the San Diego area[3]. In a population of similar demographics, over 85% of elderly subjects showed a mean PLMS Index (PLMS per hour of sleep) in excess of 5.0[4] across 5 nights of recordings. Somewhat lower estimates of

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PLMS prevalence (29.0 %) have also been reported[5]. Longitudinal data on whether PLMS increase with aging are scarce but disagree, with some studies showing increases[6] and other studies show no change[7] over time.

A substantial number of studies have examined symptomatic correlates of PLMS in middle-aged and aged populations and have shown decidedly mixed results. Complaints of poor and/or altered sleep architecture were not apparent in conjunction with PLMS in the early studies of Bixler and Kales[5, 8] and Mosko and colleagues[9]. Ancoli-Israel et al[3] noted that the myoclonus index (based solely on recorded movements without reference to EEG) was related to a history of kicking at night and some history of respiratory symptoms, but many symptoms that might be expected to be correlated with disrupted sleep (e.g., lower total sleep time, prolonged sleep onset latency) were not. The strongest single correlate of PLMS in that study was the report of the estimated number of awakenings on the night of recording. Another study in the elderly noted relationships between PLMS and sleep latency problems but not nocturnal awakenings[10]. Youngstedt et al[11] examined PLMS polysomnographically without reference to arousal and noted relationships with lower total sleep times and wake after sleep onset. By contrast, across a broader age range of subjects, Mendelson[12] evaluated leg movements accompanied by EEG arousals and was unable to find relationships between PLMS and symptoms. Montplaisir et al[13] noted no differences in PLMS among controls, individuals with insomnia and individuals with hypersomnia, and Karadeniz et al[14] found no modifications in macrosleep or microsleep architecture associated with the presence of PLMS in 40-64 year old patients with insomnia. Hornyak et al[15] reported no association between PLMS and sleep quality in non-RLS insomniac patients. More recently, Carrier et al[16] reported that the presence of PLMS was unrelated to polysomnographic measurements of sleep quality in a group of 70 normal subjects between the ages of 40 and 60, although in male subjects a significant (but very small size) effect was noted for lower sleep quality in association with PLMS Index (number of movements per sleep hour) greater than 10.

The absence of associations between subjectively and/or objectively disturbed sleep and PLMS in many of these studies stands in contrast to early published case series of patients from Sleep Disorders Clinics where the diagnosis of the condition appeared to be clearly related to disturbed sleep[17, 18]. However, these were highly selected, clinic-based populations and also included a substantial portion of patients with frank RLS, which is less ambiguously related to poor sleep and in fact, poor sleep is a feature associated with diagnosis[2] (see section below). Thus, the meaning of such studies for the clinical correlates of PLMS in the general population remains doubtful. Of note is a recent epidemiologic study suggesting that the clinical conditions of RLS and reported leg jerking may be relatively tightly coupled[19], but because PLMS in that study were defined atypically (i.e., via self-report and not electrophysiologically), it is difficult to draw inferences from these data. Some have claimed that when PLMS are defined symptomatically by the concurrent presence of sleep complaints (i.e., periodic leg movement disorder, PLMD), specific polysomnographic features (e.g., higher number of PLMS with arousal) may distinguish this group of patients from those with RLS[20].

Technical Considerations in the Recording of PLMS as a Function of Age

A possible reason that many of the aforementioned studies may have failed to find unequivocal relationships between PLMS and symptoms is the large night-to-night variability that exists in the nightly measurement of PLMS, particularly in the aged[4, 21-23]. Extensive variability in the measurement of PLMS would be expected to introduce error into the detection of any relationships between such metrics and symptoms. Potentially the variability could also underlay the inconsistencies across those few longitudinal studies to date. Factors influencing the variability in PLMS between nights remain ill-defined. Some have speculated that, in the patient with RLS, extreme variability in sleep length and/or quality may impact upon the

variability[1], such that if an individual sleeps very little on a given night their PLMS Index will be low by necessity. Some data support that the variability of the PLMS index is higher in RLS than in other sleep disorders patients[24], but higher mean levels make this conclusion equivocal on a purely statistical basis. Other studies of inter-night variability of PLMS in RLS suggest considerably less variability[25]. Considerable night-to-night variability also occurs in PLMS in elderly individuals who do not have apparent RLS, as has been noted in several studies[4, 21-23].

Several other potential age-associated aspects related to characterization of the movements have been examined. Within bouts of PLMS, both duration of movements[26] and intermovement interval (IMI)[9] were unrelated to age. Nicholas et al[26], however, noted the IMI for waking periodic leg movements decreased with age. An analysis of time of night effects noted similarly that older subjects, who had an earlier time-of-night predominance in their PLMS, also had shorter IMI's[27]. Finally, given the known disruption of sleep continuity with aging, it is hardly surprising that several studies have reported that, consistent with greater fragmentation of sleep with aging, the number of PLMS with arousals or awakening increase with age[12, 17, 28]. Heightened reactivity to movements cannot be assumed to crossover into the autonomic domain, however, since Gosselin et al[29] reported that older subjects had reduced magnitude of heart rate variability accompanying PLMS relative to younger subjects.

RLS: Prevalence and Associated Factors

RLS is a clinical syndrome, now consensually agreed upon to be defined by four cardinal features: a) the urge to move legs often accompanied by unpleasant leg sensations; b) the urge to move or unpleasant sensations begin or worsen during periods of inactivity; c) the urge to move or unpleasant sensations are relieved by movement; d) the urge to move or unpleasant sensations are worse in the evening or at night[2]. Supportive features include: positive family history, treatment responsiveness, a finding of PLMS (measured electrophysiologically).

Many[30-35] but not all[19, 36-41] epidemiologic studies have suggested that the prevalence of RLS increases with age. Interpretation of age effects in population-based work is complicated by the fact that the upper age limit varies among studies and various studies employ different definitions of RLS. The wide range of prevalence figures is depicted in Figure 1. Because of the wide range of peak prevalence (from 50-59 to as high as 80 and above) reported in these studies, it remains unclear whether RLS shows true age dependence (i.e., the likelihood of its prevalence increases nearly linearly with chronologic age), or whether the age effect is better characterized as age-related (i.e., encompassing a distinct chronologic window of vulnerability)[42]. Additionally, because these studies encompass diverse populations from the United States[32, 33, 38, 40], the United Kingdom[33, 34, 40], French and non-speaking French Canadian provinces[31], Germany[33, 37, 39, 40], Scandinavian countries[19, 30], France[35, 40], Italy[33, 36, 41] and Spain[33, 40], age differences in peak prevalence could represent the partial influence of varying genetic predispositions for RLS, consistent with several gene loci that have been implicated with the condition[43, 44].

Many conditions have been associated with RLS in these epidemiologic studies. Perhaps because many of the RLS definitions used encompass elements of disturbed sleep, only a limited number of prevalence studies have presented data on relationships between RLS and independently ascertained insomnia questions. Not surprisingly, RLS was associated with complaints of poor sleep in those studies[19, 30, 34, 40]. More commonly, medical/psychiatric conditions have been studied in association with RLS including: hypertension and cardiovascular disease[30, 33, 39], diabetes and/or possible neuropathy[32, 33, 39], depressive symptomatology[30, 34, 37] or poor mental health[32, 33], musculoskeletal disease[33], hypothyroidism[39], renal disease[34], habitual lack of exercise[32], smoking[33, 39]. Not every study

reports data on all the aforementioned conditions, and particular medication classes have also been associated with RLS (and/or PLMS) (see section below on Treatment Considerations). At least some of these conditions (e.g., cardiovascular disease depressive symptoms, diabetes, sedentary lifestyle) would be expected to occur in higher frequency in elderly populations, however there is only limited evidence that age prevalence per se could be due primarily to any one of these factors. Such a contention would require that observed age prevalence no longer occurred subsequent to multivariate adjustment for any particular associated factor. To date, no study has shown this.

Altered iron metabolism represents a condition associated with RLS deserving special note in the context of aged populations. Following the report of O'Keeffe[45] that elderly RLS patients were likely to demonstrate low serum ferritin levels, several important lines of evidence have pursued this line of work. Although frank anemia and lower serum iron may not always be apparent in association with RLS, neuroimaging and cerebrospinal fluid studies have suggested that total brain iron concentrations are reduced in RLS, which would be consistent with an alteration in blood/brain transport[46, 47]. Because anemia is a common problem in elderly populations, it is possible that such derangements in some aspect of iron metabolism underlie the high prevalence of RLS in the aged. Few studies have tested this hypothesis in elderly populations. O'Keeffe[48] published a small additional case series suggesting that serum ferritin levels <50 ng/ml were significantly more likely in elderly patients with recent onset RLS, but other population-based studies show a more complex picture. Although RLS were not accompanied by low levels of serum ferritin or by higher levels of soluble transferrin receptor in one population-based study, it appeared that mid-range levels (c.f. highest ranges) of serum iron and transferrin saturation may have exerted protective effects[49]. Neither anemia (defined by hemoglobin levels less than 2 SDs below gender- expected values) nor ferritin values were significant factors in RLS in another study of a German population across a broader age range (20-79)[39]. By contrast, in a northern Italian elderly population (South Tyrol), lower serum iron and higher soluble transferrin receptor levels (often seen in early stage anemia) were related to RLS[41]. Finally, recent data have suggested that cerebrospinal fluid (CSF) ferritin in older, late onset RLS patients were unrelated to onset of symptoms and that elderly patients had higher levels of CSF ferritin than younger patients[50]. These data cast doubt on whether iron deficiency may be a relevant risk factor for RLS presenting in the aged population, unless the condition also had early onset.

RLS in Dementia

The recent NIH Diagnosis and Workshop Conference regarding definitions of RLS[2] acknowledged that different definitions of the syndrome might be relevant in geriatrics and children. Although dementia patients may be too verbally compromised to express their condition in language, several essential features such as rubbing or kneading legs, excessive motor activity in lower limbs (including fidgeting and pacing), and worsening of leg discomfort during rest or activity and its diminishment with activity are suggestive of the condition, as is the temporally specific occurrence of leg discomfort or motor activity in the late afternoon and/or early evening. Although not explicitly described in NIH Conference Report, wandering (c.f., pacing), a widely acknowledged clinical management issue in dementia patients[51], may represent an heretofore unrecognized RLS phenotype of particular note and importance in geriatric care. For example, typical treatments for wandering may involve medications that exert dopaminergic blockage, which might otherwise be expected to worsen, rather than improve, the wandering behaviors (see section below on Treatment Considerations).

Wandering has long been recognized as one of the most difficult and intractable components of dementia in general[52] and Alzheimer's Disease (AD), specifically[53]. Patients may place themselves at grave risk wandering outside their homes, and their recovery often involves

police and other emergency service personnel[54]. Several studies have noted that nocturnal wandering was the most distressing of all sleep-related behaviors of AD patients[53, 55]. Wandering represents a particular conundrum for clinical researchers attempting to understand the mechanisms underlying these peculiar behaviors. Some descriptive research has focused on tracking the specific vectors of the ambulation[56], whereas others have focused on wandering as escape-like behavior[57]. Perhaps the most thorough neurobiologic perspective on wandering to date has been the work of Duffy and colleagues who have suggested that wandering may be a function of a modified processing system in which aberrant visual attention systems undermine spatial orientation[58, 59] or, as so aptly stated by Duffy: "Alzheimer's patients do not get lost because they have forgotten where they are going, rather, they get lost because they cannot keep track of where they have been." p. xi ref 52. Also of mechanistic interest are the positron emission tomography (PET) studies of Meguro and colleagues[60, 61], who showed that wandering AD patients (relative to those who do not wander) demonstrated lower dopamine uptake in caudate and putamen; those decreases also correlated with decreased cerebral glucose utilization in frontal and temporal, but not parietal, regions. Comparable findings have been reported more recently by Rolland et al[62]. These results in wandering AD patients bear resemblance to some neuroimaging findings in RLS patients, who showed reduced dopamine terminal storage[63, 64]. However, these parallels assume a major role for nigrostriatal dysfunction in RLS, which may be open to question (see section below on Parkinsonism).

Within the context of the NIH Workshop statement[2], there is now increasing recognition that at least some cases of wandering could represent unrecognized RLS, and the tendency for wandering to occur in the early evening hours[65] is consistent with RLS in dementia. Obviously a patient with a long-standing personal history suggestive of RLS or other (perhaps younger) family members with known RLS would also serve as partial corroboration for RLS in the dementia patient. Of note in this regard is that wanderers were more likely to have lifelong patterns of walking or strolling when stressed, at least as recalled retrospectively by family members[56]. Factors associated with RLS in the general population (anemia, diabetes, musculoskeletal disease or neuropathy), when present in a dementia patient who wanders, also might be suggestive of RLS. Curiously, as a group, AD patients were reported by their caregivers to be no more likely to have RLS symptoms or leg twitches than elderly controls[66], implying that only a subset of patients show such symptomatology. RLS patients have been reported recently to have deficits in cognitive tasks implicated in pre-frontal cortex localization, which have been interpreted as the effects of sleep loss[67]. These data can be viewed as broadly compatible with the presence of RLS in dementia.

A discussion of the phenotypic presentation of RLS in neurodegenerative disease (such as AD) invariably raises the issue of RLS in Parkinsonism, which can often but not invariably be accompanied by dementia (e.g., Lewy Body Dementia). Although RLS and Parkinsonism are both characterized broadly as dopamine deficient conditions, one could expect the prevalence of the former to be considerably higher in the latter. Some data suggest that PLMS prevalence is higher in Parkinson's Disease (PD) than in control populations[68], however, evidence to date linking PD and RLS has been negative[34, 36, 49, 69], mixed[70, 71] or, in one study, positive[72]. Low serum ferritin has been shown to a relevant mediating variable for older onset RLS in PD[70], however, as described above, there is some evidence of decreased salience of reduced iron stores as relevant for later onset RLS[50]. The relative independence of RLS and PD may reflect the relative contribution of putative postsynaptic and /or diencephalospinal dysfunction in RLS[73]. Abnormalities of flexor reflex and the sensory abnormalities accompanying RLS would be compatible with dysfunction of dopaminergic efferents and afferents within the dorsal horn that are rarely, if ever, seen in PD[73]. Comparisons of single photon emission computed tomography (SPECT) of the dopamine transporter in age-matched RLS and PD patients showed better preserved binding in the RLS patients[74]. Finally, a small neuropathologic case series of RLS patients did not demonstrate Lewy Bodies or alpha-synuclein deposits

(exceedingly common in PD), again reiterating the relative independence of the two conditions[75].

Treatment Considerations

Empirical evidence for treatment options for RLS and symptomatic PLMS (i.e., Periodic Limb Movement Disorder, PLMD) have been summarized in a Practice Parameters publication from the American Academy of Sleep Medicine (AASM) [76] and an accompanying review of empirical evidence as of 2002[77]. These publications clearly indicate the efficacy of levo-dopa and the dopamine agonists, pergolide, pramipexole and ropinirole, as effective for RLS and PLMD. Other dopamine agonists, as well as amantadine and selegiline, were viewed as possibly effective. With the exception of ropinirole (which has an FDA-approved indication for use in RLS), usage of all of these other medications constitute used off-label use. Since the publication of the AASM guidelines, a number of phase III, multi-site, randomized clinical trials of some of these medications (e.g., ropinirole) have been published that confirm the original report[78, 79]. Some data also suggest utility of dopamine agonists having longer half-lives, such as cabergoline[80], and, under development in transdermal formulation, rotigotine[81] and lisuride[82] . In practice, oral pramipexole and ropinirole probably see the most widespread current usage. The two can be distinguished by primarily hepatic (ropinirole) versus renal (pramipexole) excretion and by half-life (6 hours for ropinirole; 8-12 hours for pramipexole). Iron supplementation may also be useful in selected cases, but as suggested above, this may be less relevant for the aged population.

In the wandering dementia patient with a history of RLS or a medical condition associated with RLS, an empirical trial of a low dose dopaminergic agonist (0.25-0.5 mg ropinirole; 0.125-0.25 mg pramipexole) may represent an avenue of treatment, however, because of possible dopamine-induced psychosis, judicious usage and careful dose escalation is advised. An initial approach should examine potential exacerbating medications already in use before adding new ones. In non-demented populations, some evidence suggests that selective serotonin-reuptake inhibitors[33, 83], as well as anti-depressants such as venlafaxine[83], and mirtazapine[84, 85] can be associated with PLMD and/or RLS, though one recent study presented data to the contrary[86].

Case reports with atypical anti-psychotics (olanzapine, quetiapine, risperidone) having at least partial blockade at specific dopaminergic receptors (e.g., olanzapine at D1-D4, quetiapine at D1/D2, risperidone at D2) have been reported to both aggravate RLS or PLMS[87-89], but also treat nocturnal wandering in one case series in AD patients[90]. Neuroleptic use was significant[34] or borderline significant[37] in predicting RLS in population-based studies. At least in theory, for the dementia patient with longstanding RLS whose evening wandering and agitation represents a continuation or exacerbation of their pre-morbid condition, such medication would be expected only to aggravate, rather than improve, the behavior. In a secondary analysis of double-blind, placebo-controlled trial of risperidone in dementia patients, baseline wandering predicted higher rates of falls at 2.0 mg/day but was protective at 1.0 mg, though it was unclear whether any of the wandering patients may have represented unrecognized RLS[91]. In normal adults, quetiapine (25 mg and 100 mg) was shown to improve polysomnographically defined sleep architecture in a double-blind, placebo-controlled trial, though the number of PLMS were increased under the higher dose[92]. Taken together, these results suggest that usage of atypical anti-psychotics to treat wandering (an off-label indication) should be entertained cautiously with careful ascertainment of pre-morbid predisposition for RLS and/or PLMS.

Summary

PLMS and RLS are exceedingly common in ambulatory, non-institutionalized, non-cognitively impaired elderly populations and may occur in demented patients as well, where

they may be manifested by signs of late afternoon and evening wandering. Risk factors operating for these conditions in geriatrics include many of the same factors acknowledged to be of importance in middle-aged patients (e.g., diabetes, neuropathy/radiculopathy, renal insufficiency, cardiovascular disease) but occurring with relatively high prevalence in the elderly and thus particularly salient in this age group. Altered iron metabolism may also be a risk if the RLS is longstanding. It must never be assumed that PLMS, in the absence of frank RLS symptomatology represents a cause of poor sleep or daytime sleepiness in old age. Ample evidence demonstrates that many geriatric patients present with PLMS that have no symptomatic correlate. In such cases, intervention would be premature and unnecessary. There are no natural history data that suggest that the presence of asymptomatic PLMS is a harbinger for any later pathology, and overlap between RLS and Parkinsonism remains in doubt. Nonetheless, symptomatic RLS is a major problem for many geriatric patients and deserves full recognition as a highly treatable condition. Particularly in the dementia population with nocturnal wandering (as a potential sign of RLS) implementation of new treatment should be carefully entertained, and cessation of potentially aggravating medications always should be considered initially.

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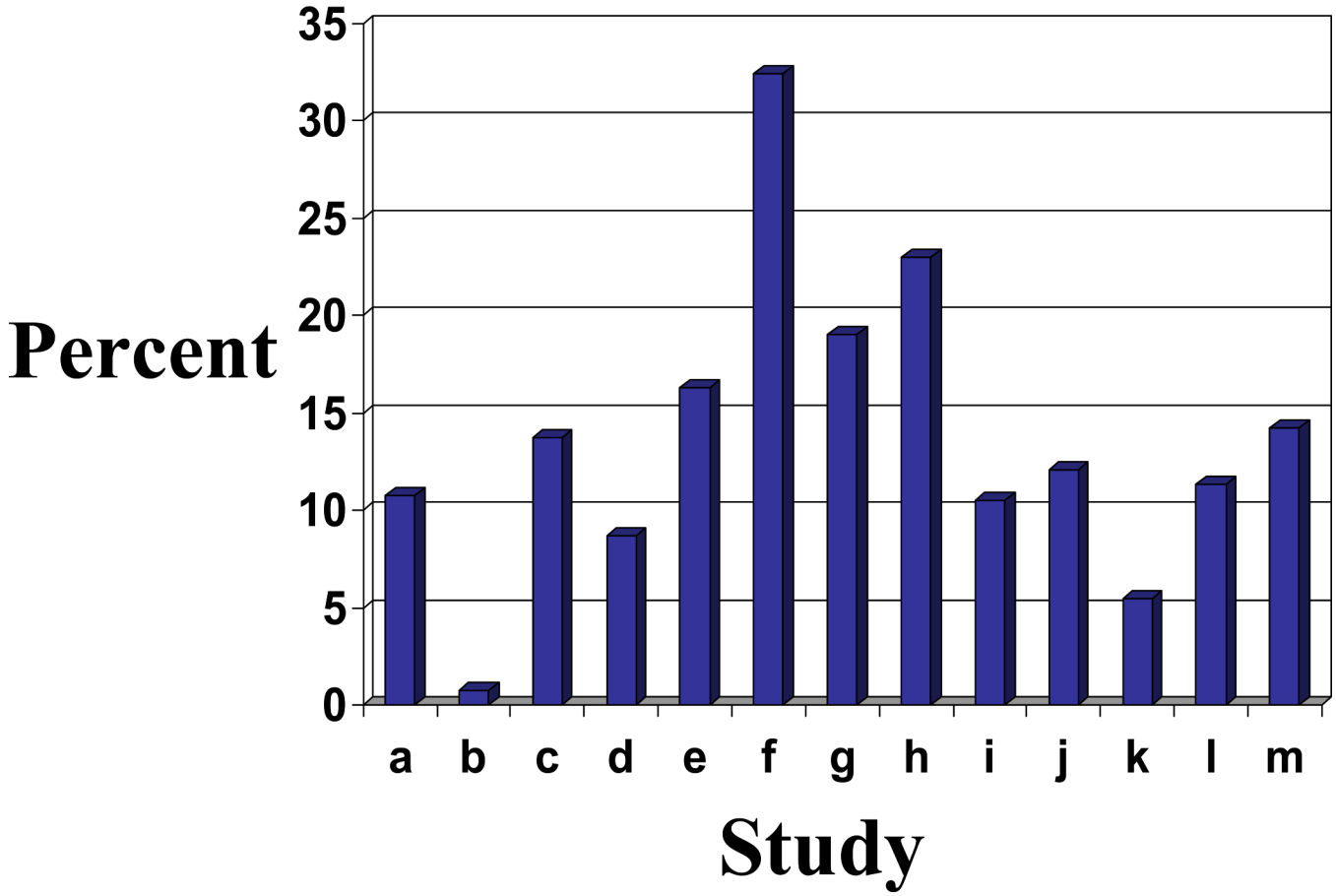

Figure 1. Prevalence of RLS Across Various Studies

Prevalence figures reflect oldest age groups with peak prevalence with data averaged for men and women when available. Studies (and references) are as follows: a[36], b [34], c [37], d[33], e[39], f[38], g[32], h[31],i[30], j[41], k[40], l[35], m[19].