

Синдром хронической усталости / миалгический энцефаломиелит: диагностика с остеопатической точки зрения

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Введение. До настоящего времени существует различный перечень симптомов CFS/ME и продолжается процесс формирования научных представлений о клинических проявлениях данного заболевания.

Цель исследования — обоснование использования остеопатического подхода в диагностике синдрома хронической усталости CFS/ME.

Материалы и методы. Проанализированы подходы к диагностике CFS/ME, проведена остеопатическая диагностика.

Результаты. Автор описывает возможный патогенез CFS/ME, который может быть понятным, если его связать с нейролимфатическими изменениями, связанными с нарушением дренажа, что приводит к дисфункции симпатической системы. В анамнезе пациентов с CFS/ME, как правило, имеются указания на наличие травмы позвоночника или врожденных проблем развития, повреждающих череп и позвоночник. Они приводят к нарушениям симпатической нервной системы вследствие гипоталамической дисфункции, заключающимся в ухудшении функционирования лимфатической системы, которое вызывает дальнейшую центральную нейротоксичность через периваскулярные пространства. В статье представлен разработанный автором протокол остеопатических признаков, характерных для пациентов с CFS/ME, и результаты диагностики 94 человек, 52 из которых имели диагноз CFS/ME и 42 — без CFS/ME. Исследование позволило сделать вывод о том, что предложенные признаки являются быстрым эффективным инструментом скрининга для CFS/ME.

Ключевые слова: синдром хронической усталости, миалгический энцефаломиелит, остеопатическая диагностика, скрининг

Chronic fatigue syndrome/myalgic encephalomyelitis: diagnosis from an osteopathic perspective

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Introduction. To date, there have existed different sets of symptoms of CFS/ME. Scientific ideas about the clinical manifestation of this disease continue to appear.

Goal of research — to justify osteopathic approach in diagnostics of CFS/ME.

Materials and methods. Analysis of approaches to the diagnostics of CFS/ME, osteopathic diagnostics.

Results. The author describes the possible pathogenesis of CFS/ME, which may be related to the neurolymphatic changes connected with the alteration of the drainage. All of this leads to dysfunctions of the sympathetic system. Medical history of patients with CFS/ME often contains indications on spinal trauma or congenital developmental disorders of the cranium and vertebral column, which may alter the function of the lymphatic system and lead to the further central neurotoxicity through perivascular spaces. The article presents a protocol of physical signs, typical for patients with CFS/ME, and the results of diagnostics of 94 patients: 52 patients with CFS/ME and 42 non-CFS/ME controls.

Conclusion. The research concluded that examining for physical signs is both quick and simple for the practitioner and may be used as an efficient screening tool for CFS/ME.

Key words: chronic fatigue syndrome, myalgic encephalomyelitis, osteopathic diagnostics, screening

Myalgic Encephalomyelitis (ME), was first termed by the then chief medical officer for The UK, Donald Acheson after two outbreaks of the illness in the 1950's at The Royal Free Hospital, London and in Iceland [1]. It took a further decade before The term «myalgic encephalomyelitis» (muscle pain, «myalgic», with «encephalomyelitis» inflammation of the brain and spinal cord) was first included by the WHO in their International Classification of Diseases in 1969.

The condition in the US was termed Chronic Fatigue Syndrome (CFS) by the Centre of Disease Control and Prevention (CDC) [2] and is characterised by «severe disabling fatigue and a combination of symptoms including disturbance in concentration and loss of short-term memory, disturbed sleep, and musculoskeletal pain» [3].

Ever since 2002 it has been referred to officially in the UK as CFS/ME following a report by the chief medical officer Sir Liam Donaldson in 2002. A disease state within the spine exists but not necessarily accompanied by inflammation so some health professionals now use the term myalgicencephalomyelopathy. A survey carried out at The University of Bristol claimed that CFS/ME affects up to 2.6 per cent of adults in Britain [4].

As there is no accepted means of diagnosis by pathological tests such as blood or urine analysis, the standard diagnostic protocol of CFS/ME used has been one of exclusion. A paper by psychiatrists at Kings College London in 2009 claimed «There are currently no investigative tools or physical signs that can confirm or refute the presence of CFS. As a result, clinicians must decide how long to keep looking for alternative explanations for fatigue before settling on a diagnosis of CFS» [5].

Internationally the most widely accepted criteria for CFS/ME was the revised US Centers for Disease Control and Prevention (CDC) definition, which required at least a 6-month period of fatigue that significantly interferes with a person's everyday activities. In addition to this, four or more of the following symptoms must have persisted or reoccurred within the last 6 months; impaired memory or concentration, postexertion malaise, sore throat, tender lymph nodes, aching or stiff muscles, joint pain, headache and unrefreshing sleep [3].

In 2007, new diagnostic guidelines were issued from the National Institute for Health and Clinical Excellence (NICE) that have remained unchanged in Britain since.

The NICE guidelines states that «CFS/ME should be considered if a person has fatigue and all of the following apply:

- there was a clear starting point;
- it is persistent and/or recurrent;
- it is unexplained by other conditions;
- it substantially reduces the amount of activity you can do;
- it feels worse after physical activity.

The person should also have one or more of these symptoms:

- difficulty sleeping, or insomnia;
- muscle or joint pain without inflammation (swelling);
- headaches;
- painful lymph nodes that are not enlarged;
- sore throat;
- poor mental function, such as difficulty thinking;
- symptoms getting worse after physical or mental exertion;
- feeling unwell or having flu-like symptoms;
- dizziness or nausea;
- heart palpitations, without heart disease.

According to NICE a clinician should confirm this diagnosis after other conditions have been ruled out and the above symptoms have persisted for four months in an adult» (NICE Clinical guidelines, CG53, 2007& 2011).

The latest internationally recognized diagnostic criteria for CFS/ME is the International Consensus Criteria [6] based on the widely adopted Canadian Criteria [7]. The Canadian criteria included many of the cardiopulmonary and neurological abnormalities, which were not included in the CDC criteria. In addition, the Canadian criteria selected cases with less psychiatric comorbidity, more physical functional impairment, more fatigue/weakness, plus neurological symptoms, which were significantly different from psychiatric controls with CFS/ME.

Over the past few years, questions have been raised by international scientists regarding the British diagnostic methods. However, there is now an ongoing review process of all the NICE guidelines so the osteopathic approach may be part of the new diagnostic procedure.

The Osteopathic Approach

A chance discovery in 1989 by the author revealed a possible association between certain biophysical dysfunctions and the incidence of CFS/ME [8,9]. The concept of CFS/ME being primarily a physical disorder is still foreign to most of the medical profession. However, many recognize that CFS/ME has physical symptoms. There are physical components within the CDC criteria mentioned above which include sore throat, tender cervical or axillary lymph nodes, myalgia, and polyarthralgia [3].

The central nervous system is the only region in the body that was always believed to contain no true lymphatic vessels. The explanation for this has been that since the blood brain barrier (BBB) prevents large molecules entering the brain there is no need for lymphatic vessels in the CNS, as cerebral blood vessels will be adequate to drain the smaller molecular structures away.

However, hormones, which are large protein molecules continually, enter the brain at the hypothalamus to enable the control of the endocrine system via the biofeedback mechanism. Therefore the blood brain barrier even if undamaged is not as impenetrable as previously thought. The gaps in the BBB allow large toxic molecules to enter the brain such as heavy metals, bacterial infections and especially pro-inflammatory cytokines. So there has to be an alternate drainage system for the brain and spinal cord to remain in good health and if this drainage system is compromised illness ensues.

As early as the 1890's, Still noted «The lymphatics are closely and universally connected with the spinal cord and all other nerves, and all drink from the waters of the brain» [10].

The Russian scientist Speransky first described the existence of a direct link between CSF and the nasal lymphatics and onwards to the cervical lymph vessels. Thus, a major drainage pathway was thought to exist involving the olfactory region has been demonstrated in mammals with many channels draining through the cribriform plate into the nasal submucosa and from there into the cervical lymph nodes. In addition, a small but significant drainage takes place via dural lymphatics, which run parallel with the spinal cord [11].

Tracer material injected into the CSF in the brain of rabbits accumulates in the cuffs around the spinal roots, which form a link between the subarachnoid spaces and the lymphatics. In rabbits it has also been shown that there is a flow of fluid from the brain to the deep lymph nodes of the neck, and a flow of fluid from the nasal mucosa to the brain [12].

In man, researchers have hypothesized that CSF can leave the CNS via several routes. As in animal studies, these include possible pathways from the cranial and spinal subarachnoid space across the arachnoid villi to the dural sinuses and along the cranial, mostly via olfactory pathways through the cribriform perforations, and spinal nerves to the lymphatics via perivascular (Virchow-Robin) spaces [13,14], *fig. 1*.

The author hypothesized that the neurolymphatic drainage becomes disturbed in CFS/ME due to dysfunctional noradrenergic sympathetic control specifically at the hypothalamus-locus coeruleus axis (*fig. 2*) [15].

In 2012 scientists at Rochester university in New York showed the first visible proof that CSF enters the parenchyma along the perivascular spaces that surround penetrating arteries and that some brain

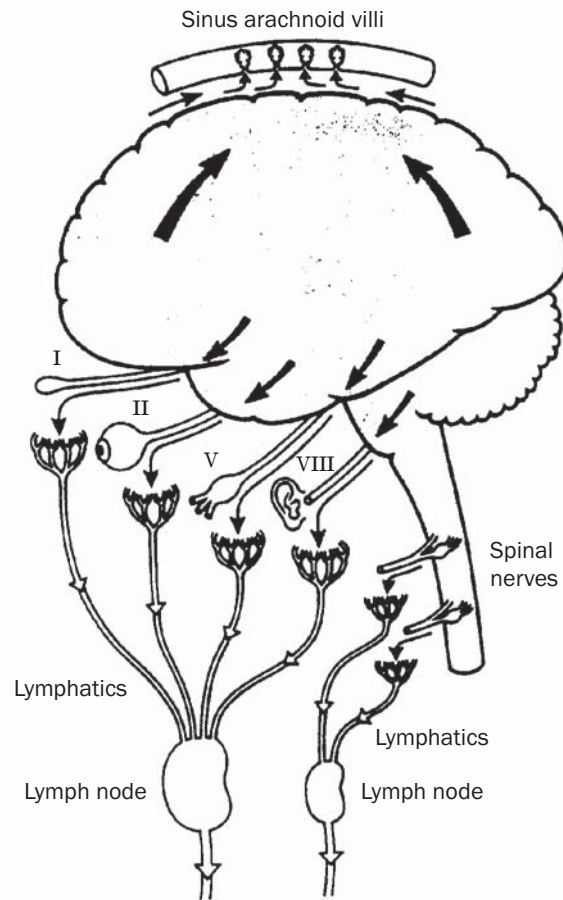


Fig. 1. Schematic demonstrating the lymphatic drainage of the human central nervous system:
I – olfactory; II – optic; V – trigeminal; VIII – acoustic [14]

interstitial fluid is cleared along paravenous drainage pathways [16]. As well as drainage into the sinus arachnoid villi there is further passage of cerebrospinal fluid (CSF) down the spine into the paravertebral lymphatics and a long side the I, II, V and VIII cranial nerves. The CSF then flows into the facial, cervical and eventually into the thoracic lymphatics. Most of the lymphatic fluid is then pumped into the blood by the sympathetic controlled, smooth muscle walls of thoracic duct via the left subclavian vein [17, 18].

Further studies on this drainage revealed it to occur mostly during delta wave sleep when the hypothalamus-locus coeruleus axis switches off [19]. Delta wave sleep, which is the deep restorative sleep, is shown to be low at night in patients with CFS/ME who have high levels of non-restorative Alpha wave sleep [20]. However, researchers at Stanford University in California have shown that in the day during the awake cycle there are high levels of delta wave in CFS/ME (Zinn & Zinn, 2013). The resultant drainage of toxins during the day would leave patients feeling fatigued and unwell. The increased activity of the hypothalamic-locus coeruleus axis at night prevents the healthy drainage and due to the effects of noradrenaline (norepinephrine) stimulation leaves patients in the state referred to as «Wired and Fired». So, this region of the brain stem is of major significance in the pathophysiological process leading to CFS/ME as suggested by Perrin (see fig. 2).

The existence of this neurolymphatic pathway has been further validated last year by a team in Virginia University in the USA [21] who discovered previously unknown lymphatic channels on the surface

of the meninges and filmed the CSF flowing from the parenchyma of the brain into these lymphatic vessels via perivascular spaces. Another group of neuroscientists in Finland published similar findings shortly after [22]. Until last year the images of the neurolymphatic system had only been produced on scans of mice brains. However, vessels in human and nonhuman primates were noninvasively imaged in vivo with high-resolution, clinical MRI. On T2-FLAIR and T1-weighted black-blood imaging, lymphatic vessels enhance with gadobutrol, showed these vessels, running alongside dural venous sinuses which matched the meningeal lymphatic system of mice [23], *fig. 3*.

The above pathway, together with a disturbance of spinal drainage of CSF to paravertebral lymphatics, is compromised as part of the common pathogenesis in CFS/ME [15, 24].

If the drainage of the brain is disturbed, what toxins are we talking about that get «stuck» in the brain?

The lymphatic system is there to drain away large molecular structures rather than small molecules which filtrate into the blood capillaries. The neurolymphatic system exists to drain large inflammatory or post infectious molecules such as cytokines and prostaglandins which may settle in the central nervous system following an infection or inflammation due to physical trauma. Recent studies in Stanford University have confirmed high levels of cytokines in the brain of CFS/ME patients with some such as Leptin correlating to symptom severity [25]. Environmental toxins can also become overloaded in CFS/ME such as heavy metals, petrochemicals and organophosphates, but a major source of neurotoxicity comes from an overstimulation of neuropeptides due to mental and emotional stress.

Central to the principles of osteopathy is the presence of a palpable cranial rhythmic impulse. The CRI is strongest along the spinal cord and around the brain and which is transmitted to the rest of the body. The average pulsation of this mechanism is between 7 and 12 beats per minute in health [26].

Three separate studies [8, 9, 15] have revealed a disturbed CRI and evidence of a retrograde, congested lymphatic system in CFS/ME patients (*fig. 4*) compared with healthy norms and that both increase in the lymphatic drainage as well as a stronger more rhythmic CRI coinciding with improvement of symptoms, supporting the view that the neurolymphatic flow is one and the same as the CRI [27]. All the physical phenomena seen in CFS/ME can be understood when the pathophysiology of the disease is viewed as being neurolymphatic in origin with impaired drainage resulting in sympathetic dysfunction.

CFS/ME patients present with a history of trauma, congenital and/or developmental problems affecting the cranium and spine (see *fig. 4*). This is also associated with other physical evidence of sympathetic nervous system disturbance due to hypothalamic dysfunction. It leads to lymphatic pump reversal causing palpable engorged varicose enlarged megalymphatics and further central neurotoxicity via the perivascular spaces.

In CFS/ME it is these drainage pathways, both in the head and the spine, that are not working sufficiently, leading to a build-up of toxins within the central nervous system. The aetiology may be traumatic, congenital and may even be hereditary. If the structural integrity of the spine and brain are both affected leading to reduced drainage, the increased toxicity (often following a viral or bacterial infection) plus stress factors (physical, chemical, emotional, immunological and/or environmental) will lead to hypothalamic dysfunction and thus affect sympathetic control of the central lymphatic vessels (Kinmonth, 1982) causing further backflow and worsening toxicity in the CNS leading to the vicious circle that we eventually call CFS/ME.

The Physical Signs: CFS/ME is very much a structural disorder with clear and diagnosable physical signs, including disturbed spinal posture (see *fig. 4*), varicose lymph vessels (*fig. 5*) and specific tender points related to sympathetic nerve disturbance and backflow of lymphatic fluid (*fig. 6*).

One independent study has indeed recently verified one of physical findings by Perrin, namely a tender point in a specific region of the left breast [28].

1. Long Standing thoracic spinal problems (Often with tenderness, erythematous and temperature changes at T4/5/6 segments). In a study carried out by pediatrician Dr. Peter Rowe and his colleagues

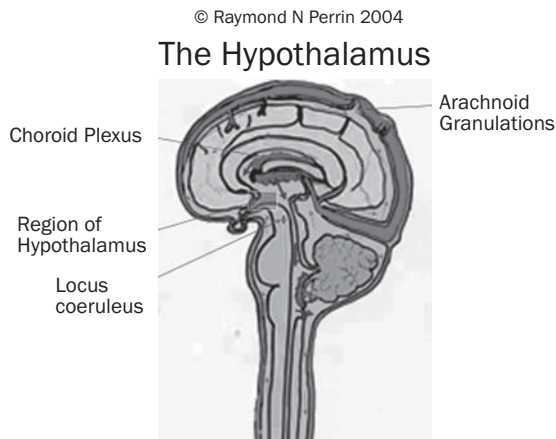


Fig. 2. The Hypothalamus, Locus Coeruleus and Cerebrospinal Fluid: The main areas of interest in the central pathophysiology leading to CFS/ME [15]

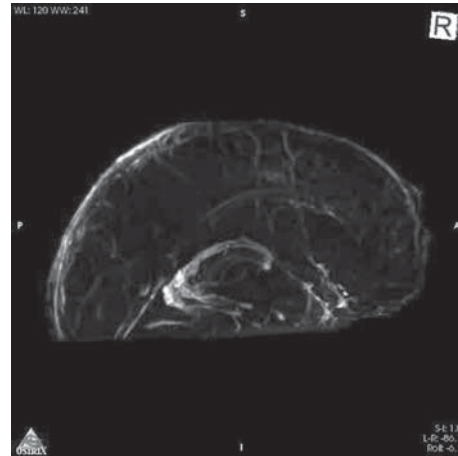


Fig 3. 3D-rendering of dural lymphatics (green) in a 47 year old woman from skull-stripped subtraction T1-black-blood images (horizontal view, 180 degrees, 7 frames/minute) [23]



Fig. 4. Lordotic mid dorsal spine with kyphotic dorso-lumbar segment (the most frequent postural disturbance found in CFS/ME patients often associated with Scheurmann's)



Fig. 5. Superficial varicose lymphatic vessels situated between right axilla and right clavicle. NB Varicose thoracic lymphatics are always palpable in CFS/ME. In this rare occasion they are clearly visible

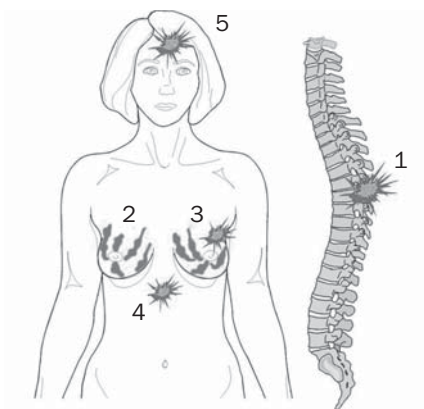


Fig. 6. The Physical Signs of CFS/ME. These signs are listed in the order of the physical examination according to the Perrin Technique protocol: 1 – long standing thoracic spinal problems (with tenderness at T4/5/6 segments); 2 – varicose lymph (megalympatics); 3 – Perrin's Point; 4 – coeliac plexus; 5 – reduction in cranio-sacral rhythm (CRI) [15, 27]

at Johns Hopkins University, Baltimore, 48 CFS/ME patients matched with healthy participants all aged between 10 and 30 were shown to have increased thoracic kyphosis and lumbar lordosis with localised impairments in the range of movements in the limbs and the spine. In an international CFS/ME conference in San Francisco in 2014 when asked about mid-thoracic flattening and stiffness originally observed by Dr Perrin he replied «Yes we also see this.....and it is usually associated to the hypermobility of the cervical and lumbar region».

2. Varicose enlarged lymph vessels: due to a reversal of the sympathetically controlled thoracic duct pump.

3. Tenderness at Perrin's Point. The connection between peripheral somatic nociceptive afferent fibres and sympathetic nerves has been observed in pathological mechanisms [29].

Sympathetic influence has been noted via:

- noradrenalin directly on peripheral afferent via alpha 1 adrenergic receptors;
- noradrenalin exciting alpha 2 adrenergic receptors mediating the release of prostaglandins exciting the primary afferent fibre;
- sympathetic and sensory fibres coupled electrically via synapses or the lesser known ephapsis resulting in 'cross talk' along the axons themselves [30];
- noradrenalin release may have local effects on blood flow, environment in skin enhancing activity.

While many autonomic nerves are purely sensory, certain primary afferent nerve fibres also have an efferent (and trophic) function. Sensory neurotoxins stimulate transmitters released at peripheral endings to produce vasodilation and smooth muscle contractility. Furthermore, they may have effects on the regional leukocytes and fibroblasts leading to what is known as «neurogenic inflammation», with eventual stimulation of somatic afferent fibres causing pain [31]. This may explain many of the more severe musculo-skeletal and sensory symptoms affecting the patient with CFS/ME.

Fibromyalgia is viewed by many as sharing the same pathophysiology as CFS/ME with widespread pain in all four quadrants being the principal symptom. New evidence from biopsy has revealed a major source of pain in fibromyalgia, is due to an increase in sympathetico-sensory innervation [32].

Dizziness, palpitations and orthostatic hypotension are common symptoms of CFS/ME and may relate to cardiac plexus dysfunction. We also know due to the reversal of lymph flow and formation of varicose megalymphatics that the sympathetic control of the smooth muscle wall of the thoracic duct is disturbed.

Therefore due to viscerosomatic crosstalk from dysfunctional sympathetic control of the thoracic duct and disturbed cardiac plexus, a hypersensitive region slightly lateral and superior to the left nipple develops. This tender spot (also known as Perrin's point), has been already independently verified in a controlled trial [15, 27, 28, 33].

4. Tenderness of the Coeliac Plexus: in cases when there are abdominal symptoms such as IBS, lower thoracic, lumbar, pelvic or lower extremity pain, the coeliac plexus will become overactive and more sensitive due to similar reasons for Perrin's point.

5. A disturbance in the regular cranio-sacral rhythm (CRI/IVM): with a palpable loss of vitality, the severity of which is often related to the overall symptom picture. Based on his prior work, this flow is believed by Dr Perrin to be most likely the drainage of cerebrospinal fluid into the pumping thoracic duct of the lymphatic system [24].

The diagnostic technique based on the NICE guidelines is an imperfect reference standard but is the best available to the NHS at present. However, following the first oral hearing on Tuesday 18th April 2006 of the Gibson Enquiry at the House of Commons, it was generally concluded by those present that an earlier diagnosis would usually lead to a better prognosis when treating CFS/ME. The published report from the Gibson enquiry of Nov 2006, described The Perrin Technique as «a useful and empirical method which although unorthodox should not be dismissed as unscientific and that it required further research» [34].

A quicker diagnosis would reduce the huge financial burden placed on health services around the world by reducing the need of some of the specialist services used and the pathological tests carried out at present. In this respect new research was carried out at the University of Central Lancashire in conjunction with 2 major hospitals in the North West of the UK published in the BMJ Open [35].

In this study which was a blind controlled trial there were two practitioners who examined the participants for physical signs as an aid to diagnosis.

The examination was performed by two Allied Health Professions AHPs. One had 10 years of experience of using the Perrin technique and working with patients with CFS/ME (experienced AHP); the other was newly trained in the Perrin technique with no prior experience of CFS/ME (newly trained AHP). The newly trained AHP received training, especially for this study, which involved being taught how to examine patients for the five physical signs and having hand-on experience of practicing the technique.

A standard clinical neurological and rheumatological assessment was performed by a physician while observing the participant for any signs of illness behaviour, but no conversation took place with the participants and no clinical history was taken by any of the practitioners involved.

Ninety-four participants were recruited: 52 patients with CFS/ME and 42 non-CFS/ME controls. The AHP experienced in the Perrin technique was able to identify 88% of patients with CFS/ME using all five physical signs with an overall accuracy of 85% when both practitioners results were taken into account.

When using the standard clinical neurological and rheumatological examination, the sensitivity of the physician was 0.44 (95% CI 0.30 to 0.59) and the specificity was 1.0 (95% CI 0.92 to 1.0). These results show that while able to identify correctly all healthy controls, the physician struggled the most out of all three practitioners to identify correctly people with a positive diagnosis of CFS/ME.

Conclusion

Standard clinical examination is not a useful modality for confirming diagnosis of CFS/ME even by a specialist in this field. This research showed that more than half of patients with CFS/ME do not look ill and do not display any evidence of illness behavior, which demonstrated clearly the need for a better diagnostic tool that is provided by the physical osteopathic diagnostic methods developed by the author. The research concluded that examining for physical signs is both quick and simple for the practitioner and may be used as an efficient screening tool for CFS/ME. This study did not include patient/family history or the patient talking about their symptoms, which should increase accuracy in clinical practice [35].

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