ASSOCIATED CONDITIONS

Carcinoid tumour associated with enterovirus infection

• John Chia,
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• Case report

Abstract

Enteroviruses commonly infect the gastrointestinal tract, and replication of enteroviruses has been well
documented in the Peyer patches of the small bowel. Chronic enterovirus infection has been found in the
stomach and terminal ileum of patients with myalgic encephalomyelitis/chronic fatigue syndrome. The authors
report the unexpected finding of enterovirus VP1 protein, by immunoperoxidase staining, in carcinoid
tumours found in one patient with myalgic encephalomyelitis/chronic fatigue syndrome and another patient
with chronic lower quadrant abdominal pain, and suggest a possible association between enteroviruses and
tumorigenesis.

Modafinil ameliorates excessive daytime sleepiness after traumatic brain injury

Authors: Kaiser PR et al

Summary: This pilot study evaluated the effects of
modafinil treatment in patients with excessive daytime
sleepiness (EDS) and fatigue after traumatic brain injury
(TBI). 20 patients who had fatigue and/or EDS after
TBI were randomised to receive placebo or modafinil
100-200mg each morning for 6 weeks in a doubleblind
manner. Sleepiness and fatigue were assessed
at baseline and 6 weeks. EDS (assessed using the
Epworth Sleepiness Scale) and the ability to stay awake
(assessed using the Maintenance of Wakefulness Test)
improved significantly in modafinil recipients compared
with placebo recipients after 6 weeks. Neither modafinil
nor placebo had any effects on post-traumatic fatigue.
In conclusion, modafinil was effective and well tolerated
in patients with post-traumatic EDS but had no effects
on fatigue.

Comment: This is an only slightly satisfying study.
While sleepiness is a problem for a few patients
post head injury, fatigue is much more common.
Along with headaches, poor concentration, irritability
and dizziness, fatigue forms part of the puzzling and
treatment-resistant post-concussion syndrome. While
most patients improve with time, a proportion make
very little progress and the symptoms remain a burden
for themselves, their family and the health system.

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Tricyclic antidepressants and headaches: systematic review
and meta-analysis

Authors: Jackson JL et al

Summary: This review and meta-analysis evaluated the efficacy and tolerability of tricyclic antidepressants in
patients with migraine, tension-type, and mixed headaches. 37 randomised trials of tricyclics in adults with headache
treated for ≥4 weeks were identified. Tricyclics significantly reduced the number of days with tension-type
headache (average standardised mean difference $\bar{\Delta} = 1.29$, 95% CI $\bar{\Delta} = 2.18$ to $-0.39$) and the number of headache attacks from migraine ($\bar{\Delta} = 0.70$, 95% CI $\bar{\Delta} = 0.93$ to $-0.48$) compared with placebo but not compared with selective serotonin reuptake inhibitors (SSRIs). The effect of tricyclics increased as the duration of treatment increased. Tricyclics significantly reduced the intensity of tension-type headache compared with placebo (RR 1.41, 95% CI $1.02$–$1.89$) and SSRIs (RR 1.73, 95% CI $1.34$–$2.22$) and the intensity of migraine compared with placebo (RR 1.80, 95% CI $1.24$–$2.62$) and SSRIs (RR 1.72, 95% CI $1.15$–$2.55$), Tricyclics caused more adverse events than placebo and SSRIs, including dry mouth ($p < 0.0005$), drowsiness ($p < 0.0005$) and weight gain ($p < 0.001$). In conclusion, tricyclic antidepressants effectively prevent migraine and tension-type headaches.

Comment: It is worth reminding ourselves that tricyclic antidepressants do work for benign headache (migraine and tension-type headache). The trick is to introduce them slowly, and patiently and persistently get the dose up, preferably to around 75mg per day. We often see patients who abandon the tricyclics early because of side effects or lack of efficacy. This study reinforces our advice to patients to keep trying as benefit may not accrue until 4-6 weeks have passed.

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Spatial versus verbal memory impairments in patients with fibromyalgia.

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Abstract

Mounting evidence suggests that individuals with fibromyalgia (FM) have impairments in general cognitive functions.

However, few studies have explored the possibility of dissociation between verbal and visuospatial memory impairments in FM. Therefore, the purpose of this study was to investigate the asymmetrical impairment of cognitive functions between verbal and visuospatial memory and between short-term and long-term memory.

Neuropsychological assessments were carried out on 23 female patients with FM and 24 healthy female controls. Verbal memory abilities were assessed using the Korean version of the Rey auditory verbal learning test (KAVLT) and digit span task, and visuospatial memory abilities were assessed using the Korean version of the Rey complex figure test (KCFT) and spatial span task.

The analysis of covariance was used to assess group differences in performance on cognitive tests after controlling for depression. The two groups did not significantly differ in terms of age, years of education, or in their estimated verbal and performance IQ, but FM patients reported more severe depressive symptoms than did controls on the Beck depression inventory.

Significant group differences were found in immediate and delayed recall on the KCFT (F (1,44) = 6.49, $p = 0.014$ and F (1,44) = 6.96, $p = 0.011$, respectively), whereas no difference was found in immediate and delayed recall on the KAVLT. In terms of short-term memory, neither the digit span task nor spatial span task showed any difference between groups, regardless of whether repetition was forward or backward.

These findings suggest that spatial memory abilities may be more impaired than verbal memory abilities in patients with FM.

Systematic Review of the Comparative Effectiveness of Antiepileptic Drugs for Fibromyalgia.


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Abstract

Fibromyalgia is a difficult-to-treat chronic pain syndrome that affects 2% of the US population.

Pregabalin is an antiepileptic recently FDA approved for fibromyalgia treatment. Other antiepileptics have been suggested for treatment.

This systematic review examines the relative benefits and harms of antiepileptic drugs in the
A literature search was conducted and 8 studies matched criteria (7 studies of pregabalin, 1 of gabapentin). Both drugs reduced mean pain scores more than placebo at a modest rate (pregabalin, 38% to 50%; gabapentin, 51%). In a 6-month trial of pregabalin responders, 32% continued to have response at 6 months, with a mean time to loss of response of 34 days.

Compared to placebo, the drugs had similarly high rates of adverse events and withdrawals. Without a head-to-head trial it is not possible to conclude if 1 antiepileptic is more effective or harmful than the other, although limited evidence suggests potential differences.

Future studies must directly compare the drugs, include a more broadly defined population, examine long term benefits and harms, and include cointerventions. We conclude that pregabalin and gabapentin are modestly effective for the treatment of fibromyalgia but that their long-term safety and efficacy remain unknown.

**Perspective:** This systematic review evaluates the benefits and harms of using the antiepileptic drugs gabapentin and pregabalin for the treatment of fibromyalgia. Conclusions from this paper can help clinicians to more effectively treat the pain associated with fibromyalgia.

GRAY MATTER VOLUMES OF PAIN-RELATED BRAIN AREAS ARE DECREASED IN FIBROMYALGIA SYNDROME.


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Abstract

Fibromyalgia (FM) is a chronic, widespread musculoskeletal pain disorder that is very prevalent in the general population (approximately 5%).

Accumulating evidence suggests that FM is associated with central pain processing abnormalities, ie, central sensitization.

Several previous studies of chronic pain patients, including FM, have shown gray matter atrophy of brain areas associated with sensory and affective pain processing. These findings, however, have not been confirmed in all FM studies.

In this study, we investigated gray matter volumes of brain areas associated with pain-related areas of FM patients identified by functional brain imaging.

Using voxel-based morphometric (VBM) analysis of magnetic resonance brain images, we compared 19 pain-related brain areas of 14 female FM patients and 11 healthy controls (NC).

We found that FM patients had significantly less gray matter volumes than NC in 3 of these brain regions, including the anterior and mid-cingulate, as well as mid-insular cortices.

Importantly, FM patients demonstrated neither global gray matter atrophy nor gray matter changes associated with depression, as shown in some studies.

Using a more stringent analysis than other VBM studies, we provide evidence for decreased gray matter volumes in a number of pain-related brain areas in FM. Although the mechanisms for these gray matter changes are presently unclear, they may contribute to some of the core features of this chronic disorder including affective disturbances and chronic widespread pain.

**Perspective:** Increasing evidence supports the association of chronic pain with accelerated
gray matter atrophy in pain disorders like low back pain, IBS, and FM syndrome. However, cause-effect relationships between chronic pain and decreased gray matter volumes have not been established yet and will require future prospective studies.

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Abstract

OBJECTIVE: To develop a fibromyalgia (FM) survey questionnaire for epidemiologic and clinical studies using a modification of the 2010 American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia (ACR 2010). We also created a new FM symptom scale to further characterize FM severity.

METHODS: The ACR 2010 consists of 2 scales, the Widespread Pain Index (WPI) and the Symptom Severity (SS) scale. We modified these ACR 2010 criteria by eliminating the physician's estimate of the extent of somatic symptoms and substituting the sum of 3 specific self-reported symptoms. We also created a 0-31 FM Symptom scale (FS) by adding the WPI to the modified SS scale. We administered the questionnaire to 729 patients previously diagnosed with FM, 845 with osteoarthritis (OA) or with other noninflammatory rheumatic conditions, 439 with systemic lupus erythematosus (SLE), and 5210 with rheumatoid arthritis (RA).

RESULTS: The modified ACR 2010 criteria were satisfied by 60% with a prior diagnosis of FM, 21.1% with RA, 16.8% with OA, and 36.7% with SLE. The criteria properly identified diagnostic groups based on FM severity variables. An FS score ≥ 13 best separated criteria+ and criteria- patients, classifying 93.0% correctly, with a sensitivity of 96.6% and a specificity of 91.8% in the study population.

CONCLUSION: A modification to the ACR 2010 criteria will allow their use in epidemiologic and clinical studies without the requirement for an examiner. The criteria are simple to use and administer, but they are not to be used for self-diagnosis. The FS may have wide utility beyond the bounds of FM, including substitution for widespread pain in epidemiological studies.

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Do We Need Core Sets of Fibromyalgia Domains? The Assessment of Fibromyalgia (and Other Rheumatic Disorders) in Clinical Practice.

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Abstract

OBJECTIVE: An OMERACT consensus process recommended domains for investigation in fibromyalgia (FM) clinical trials. We used patient data to investigate variable importance in the
determination of patient global and health-related quality of life (HRQOL) in FM and non-FM patients to determine whether variables were valued differently in FM compared with non-FM states.

METHODS: We used ACR 2010 diagnostic FM criteria modified for epidemiological and clinical research to identify patients with rheumatoid arthritis (RA; N = 5884) with and without FM, and also characterized previously diagnosed patients with FM (N = 808) as to current criteria status. We measured variable importance by multivariable regression, decomposing regression variance by averaging over model orderings. We examined the distributions of key variables in the various disorders, and the distributions as a function of a FM severity index (fibromyalgianess).

RESULTS: Out of 9 measures, pain, Health Assessment Questionnaire disability index, and fatigue explained more than 50% of explainable variance (50.49%-56.59%). Explained variance was similar across all disorders and diagnostic groups. In addition, the SF-36 physical component summary score varied across disorders as a function of fibromyalgianess.

CONCLUSION: The main determinants of global severity and HRQOL in FM are pain, function, and fatigue. But these variables are also the main determinants in RA and other rheumatic diseases. The content and impact of FM, whether measured by discrete variables or a fibromyalgianess scale, seems to be independent of diagnosis. These data argue for a common set of variables rather than disease-specific variables. Clinical use is supported and enhanced by simple measures.

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Asymmetric dimethylarginine (ADMA) levels are increased in patients with fibromyalgia: Correlation with Tumor necrosis factor-α (TNF-α) and 8-iso-Prostaglandin F(2α) (8-iso-PGF(2α)).

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Abstract

Objective The aim of the study was to investigate serum levels of asymmetric dimethylarginine (ADMA), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and plasma levels of 8-iso-prostaglandin F(2α) (8-iso-PGF(2α)) in patients with fibromyalgia. Design and method 27 patients with fibromyalgia and 20 healthy controls were enrolled in this study. ADMA, TNF-α, IL-6 and 8-iso-PGF(2α), levels were measured by enzyme-linked immunosorbent assay (ELISA).

RESULTS: Serum levels of ADMA and TNF-α and plasma levels 8-iso-PGF(2α) were significantly increased in patients with fibromyalgia compared to controls. However, no significant difference was observed in IL-6 levels between the two groups. ADMA concentrations were positively correlated with TNF-α and 8-iso-PGF(2α) levels in patients with fibromyalgia.

CONCLUSION: This is the first study reporting that ADMA levels are significantly elevated in patients with fibromyalgia in association with increased 8-iso-PGF(2α) and TNF-α concentrations. Thereby, ADMA could be suggested as a reliable marker of endothelial dysfunction in patients with fibromyalgia.

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Given the increasing evidence supporting the clinical significance of central sensitization in those with unexplained chronic pain, the awareness is growing that central sensitization should be a treatment target in these patients.

Areas covered: This article provides an overview of the treatment options available for desensitizing the CNS in patients with chronic pain due to central sensitization. It focuses on those strategies that specifically target pathophysiological mechanisms known to be involved in central sensitization.

In addition, pharmacological options, rehabilitation and neurotechnology options are discussed. Expert opinion: Acetaminophen, serotonin-reuptake inhibitor drugs, selective and balanced serototin and norepinephrine-reuptake inhibitor drugs, the serotonin precursor tryptophan, opioids, N-methyl-d-aspartate (NMDA)-receptor antagonists, calcium-channel alpha(2)delta (a2δ) ligands, transcranial magnetic stimulation, transcutaneous electric nerve stimulation (TENS), manual therapy and stress
management each target central pain processing mechanisms in animals that - theoretically -
desensitize the CNS in humans.

To provide a comprehensive treatment for 'unexplained' chronic pain disorders characterized by
central sensitization, it is advocated to combine the best evidence available with treatment
modalities known to target central sensitization.

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Factors associated with co-morbid irritable bowel syndrome and chronic fatigue-like symptoms in
functional dyspepsia.
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Abstract

Background: It is unclear which factors explain the high co-morbidity between functional dyspepsia
(FD) and other functional somatic syndromes.

The aim of this study is to investigate the association between gastric sensorimotor function,
psychosocial factors and 'somatization'
on the one hand, and co-morbid irritable bowel syndrome (IBS) and chronic fatigue (CF)-like
symptoms on the other, in FD.

Methods In 259 tertiary care FD patients, we studied gastric sensorimotor function with barostat
(sensitivity, accommodation). We measured psychosocial factors (abuse history, alexithymia, trait
anxiety, depression, panic disorder) and 'somatization' using self-report questionnaires, and
presence of IBS and CF-like symptoms.

Hierarchical multiple logistic regression was used to determine which of these factors were
independently associated with co-morbid IBS and CF-like symptoms, including testing of potential
mediator effects.

Key Results Co-morbid IBS or CF-like symptoms respectively were found in 142 (56.8%) and 102
(39.4%) patients; both co-morbidities were not significantly associated (P = 0.27). Gastric
accommodation (β = 0.003, P = 0.04) and 'somatization' (β = 0.17, P = 0.0003) were
independent risk factors for IBS (c = 0.74, P < 0.0001); the effect of adult abuse (β =
0.72, P = 0.20) was mediated by 'somatization'. Depression (β = 0.16, P = 0.008) and
'somatization' (β = 0.18, P = 0.004) were overlapping risk factors for CF-like symptoms (c
= 0.83, P < 0.0001); the effects of alexithymia and lifetime abuse were mediated by
depression and 'somatization', respectively.

Conclusions & Inferences 'Somatization' is a common risk factor for co-morbid IBS and CF-like
symptoms in FD and mediates the effect of abuse. Gastric sensorimotor function and depression
are specific risk factors for co-morbid IBS and CF-like symptoms, respectively.

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Autonomic cardiovascular control and responses to experimental pain stimulation in fibromyalgia
syndrome.

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Abstract
OBJECTIVE: This study involves a comprehensive investigation of autonomic cardiovascular regulation in fibromyalgia syndrome (FMS) at rest and during painful stimulation and its association with pain indices.

METHODS: In 35 patients and 29 healthy controls, electrocardiography, impedance cardiography, and finger continuous blood pressure measurements were conducted. For the purpose of experimental pain induction, a cold pressor test was applied.

RESULTS: FMS patients showed lower pain threshold and tolerance, as well as higher ratings of pain intensity and unpleasantness on visual analogue scales.

Resting stroke volume, myocardial contractility, R-R interval, heart rate variability, and sensitivity of the cardiac baroreflex were reduced in the patients, and increases in stroke volume and myocardial contractility during cold pressor stimulation were less pronounced. In the whole sample as well as in the FMS group, baroreflex sensitivity was inversely associated with subjective pain intensity, and a higher number of baroreflex operations per unit of time predicted higher pain tolerance.

CONCLUSIONS: The data suggest impaired autonomic cardiovascular regulation in FMS in terms of reduced sympathetic and parasympathetic influences, as well as blunted sympathetic reactivity to acute stress.

The association between baroreflex function and pain experience reflects the pain inhibition mediated by the baroreceptor system.

Given the reduced baroreflex sensitivity in FMS, one may assume deficient ascending pain inhibition arising from the cardiovascular system, which may contribute to the exaggerated pain sensitivity of FMS.

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Pregabalin in Treatment-Refractory Fibromyalgia.

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Abstract

CONTEXT: Fibromyalgia is a chronic musculoskeletal pain disorder. The pain can be intractable and may not respond to commonly-used treatments, such as tricyclic antidepressants and opioids.

OBJECTIVES: To evaluate pregabalin response in the subset of patients with fibromyalgia whose pain had been judged refractory to other treatments.

METHODS: Patients had previously participated in a controlled trial of pregabalin and had moderate to severe pain despite treatment with gabapentin, a tricyclic antidepressant, and a third medication (e.g., other anticonvulsants, opioid, selective serotonin reuptake inhibitors, tramadol). Flexible-dose pregabalin 150-600 mg/day was added for 3-month treatment cycles, each followed by 3- to 28-day pregabalin "drug holiday" that lasted until a relapse occurred. Pain intensity was measured using the visual analogue scale of the Short-Form McGill Pain Questionnaire completed at baseline, the end of each 3-month treatment period and at the relapse visit. Analysis was at 15 months (after 5 cycles).

RESULTS: In total, 25 patients were included and 19 completed the 15-month analysis period. At baseline, 88% were receiving ≥1 pain medication. Pregabalin 150-600 mg/day was associated with statistically significant, clinically meaningful pain reduction during each treatment cycle. Pain quickly returned to baseline levels during the "drug holidays" in a median time of 2-4 days. Somnolence (n=5) and dizziness (n=4) were the most common adverse events.

CONCLUSIONS: These results suggest that pregabalin may be beneficial in patients with fibromyalgia who have had an unsatisfactory response to treatment with other medications.
Arterial stiffness and proinflammatory cytokines in fibromyalgia syndrome.

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Abstract

OBJECTIVES: We assessed arterial stiffness and inflammatory cytokine profiles in fibromyalgia syndrome (FMS) patients and analysed the association between them.

METHODS: Twenty-seven FMS patients and 29 age-matched premenopausal healthy controls were enrolled in this study. Arterial stiffness was assessed by pulse wave velocity (PWV) and augmentation index (AIx) from pulse waveform analysis. Levels of serum interleukin-1β (IL-1β), IL-6, IL-8, and vascular endothelial growth factor (VEGF) were measured by enzyme-linked immunosorbent assay, and a colorimetric assay was used for measurement of serum nitric oxide (NO) metabolites (nitrate and nitrite, NOx) level. Statistical analyses included the Mann-Whitney U-test and Spearman's correlation coefficient analysis.

RESULTS: Higher AIx and AIx@HR75 (aortic AIx at a heart rate of 75 beats/min) were noted in FMS compared to those in the controls after adjustment using covariants (p(adj)=0.023 and p(adj)<0.001). However, there were no differences between the three regional PWVs of the two groups at the aorta-femoral, femoral-dorsalis, and aorta-radialis arteries (p(adj)>0.05 for all). FMS subjects had significantly higher serum IL-8 levels than did the healthy controls (327.9±588.7 vs. 76.4±90.5, p(adj)=0.041). However, there were no significant differences in serum IL-1β, IL-6, VEGF, or NOx levels between the FMS patients and the controls (p(adj)>0.05 of all). Serum IL-8 level did not correlate with PWV and AIx in FMS patients.

CONCLUSIONS: This study demonstrates higher AIx and IL-8 levels in FMS subjects compared to those of the controls. However, arterial stiffness including AIx in FMS was not determined by the serum IL-8 level.

Will vitamin D supplementation ameliorate diseases characterized by chronic inflammation and fatigue?

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Summary
Chronic NF-κB activation has been supposed as a key event in chronic fatigue syndrome (CFS) and many other better-defined pro-inflammatory diseases. Knowledge about the impact of deficiency vitamin D on chronic NF-κB activation could open a new disease approach. Whereas NF-κB activation leads at first to a pro-inflammatory immune response, later on a vitamin D-dependent anti-inflammatory response ensues. Binding of the active vitamin D metabolite 1,25(OH)2D3 to vitamin D receptor (VDR) yields a transcription factor which represses NF-κB activation, and additionally modulates and down-regulates adaptive, but enhances innate immune responses, and improves redox balance, thus counterbalancing inflammation on multiple levels. However,
this built-in late counterbalance against inflammation works only when stores of calcium and 25(OH)D3 are abundant. Therefore a connection between lowered vitamin D-metabolism and persistent NF-κB activation, augmented nitrosative-oxidative stress, redox imbalance, chronic inflammation, and concomitant fatigue can be postulated. In order to confirm this hypothesis, randomized controlled clinical studies about the clinical effects of supplementation of calcium and vitamin D3 would be necessary in diseases characterized by persistent NF-κB activation and chronic inflammation and fatigue. Published in Medical Hypotheses - 2010 Elsevier Ltd. All rights reserved. www.sciencedirect.com