HIV-1 Evolution under Low CCR5 Selection Pressure

Anjali Joshi, PhD

Introduction

CCR5 co-receptor expression levels play an important role in HIV infection and pathogenesis by regulating virus entry and disease progression. This is related to the CCR5 expression levels in the host which is regulated both via CCR5 gene and promoter polymorphisms. While CCR5 levels play a complex role in HIV infection and disease progression, it remains unknown how HIV evolves in the presence of varying CCR5 levels.

Materials and Methods

Long term HIV replication studies were conducted in T cells lines expressing different levels of CCR5. Virus evolution was monitored genotypically via sequencing and phenotypically for various virion characteristics like co-receptor switch, changes in CD4/co-receptor binding affinity, altered fusion capacity, resistance to Maraviroc and changes in the virion infectivity in the presence of low CCR5 levels.

Results

HIV replication studies in T cells expressing low levels of CCR5 resulted in the emergence of an adapted virus harboring the mutations E170K in V2 loop and N298Y in the V3 loop. The adapted virus maintained CCR5 tropism while exhibiting an increase in Maraviroc IC50 presumably by evolving higher affinity for CD4 and/or CCR5. Changes in the V2 and V3 loop may be important in predisposing the virus to co-receptor switch.

Conclusions

HIV adaptation to low CCR5 levels may drive the virus towards CXCR4 usage via an intermediate phenotype that maintains CCR5 tropism and renders the virus more fit in the presence of low co-receptor levels.

Protocol for Early Detection and Treatment of Schizophrenia in Children and Adolescents

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Introduction

Detection of early developing psychotic illnesses in children and adolescents could be quite challenging. However, different non-psychotic symptoms that usually arise during the early prodromal phase of the disease, for example early cognitive decline, can be helpful for the early detection and subsequently to a chronic illness, where early intervention could improve the long term prognosis.

Materials and Methods

1. Patients inclusions: criteria of inclusions and referrals
2. Assessment for schizophrenia/schizoaffective: clinical, psychometric, structured interviewing and neuropsychological testing, functional imaging
3. Treatment of diagnosed case: education, medication, therapy (individual, group and family)
4. Long term follow up of cases to recognize different patterns

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of early presentations and effectiveness of different treatment interventions.

Results

Goals-
1. Detection of early onset schizophrenia at its prodromal stage
2. Providing treatment early in course to improve long term prognosis
3. Raising the standards of mental health services for children and adolescents in the great El Paso area.

Pulmonary Thromboembolism as a Complication of Systemic Lupus Erythematosus and Antiphospholipid Syndrome

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Introduction

Antiphospholipid syndrome (APS) is characterized by antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies) in the presence of arterial or venous thrombosis. These autoantibodies are often detected in systemic lupus erythematosus (SLE), and thus APS and SLE may coexist. APS may lead to pulmonary manifestations such as thromboembolism and pulmonary hypertension. While acute pulmonary thromboembolism is a more common presentation, chronic thromboembolism only occurs in a small percentage of patients with antiphospholipid antibodies.

Materials and Methods

We present a case of a 47 year old female who presented with chronic pulmonary thromboembolism as a complication of SLE and APS. The results from the laboratory, serology and imaging tests performed were used for the diagnosis and management of this patient’s condition. She was under the care of our medical team at University Medical Center. No personal identification information was used nor was it necessary for this care report.

Results/Conclusions

Chronic pulmonary thromboembolism is a rare initial presentation as a complication of APS and coexisting SLE. We have presented a case of a 47 year old female with chronic pulmonary thromboembolism with no prior medical history. She was then diagnosed with APS and SLE based on positive serologic results. She was placed on long term oral anticoagulation as prophylactic treatment for recurrent thrombosis to prevent further complications such as chronic pulmonary hypertension. Chronic thromboembolism frequently causes progressive pulmonary hypertension in APS and has a poor prognosis. Therefore, early diagnosis and intervention is necessary to prevent further long-term complications and improve prognosis.

Effect of Moderate Exercise in Diabetic Neuropathy

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Introduction

Peripheral neuropathy is a significant complication of diabetes and it interferes with the quality of life. Unfortunately, available medical treatment is relatively ineffective. Emerging research indicates that moderate physical activity provides health-related benefits. Previously we have shown that proinflammatory cytokines play a role in pain perception. In this study, we found that regular exercise decreased painful neuropathy in the Type 1 model of diabetic (T1D) animals by reducing inflammation in the nervous system.

Materials and Methods

T1D animals were placed in motorized running wheels for 60 min/day, 5 days/week for six weeks. Behavioral measures of thermal pain threshold, cold allodynia and mechanical hyperalgesia were performed at two-weeks intervals. Finally, animals were euthanized for analysis of inflammatory mediators.

Results

There was a decrease in mechanical pain threshold in the diabetic sedentary group compared to control group and it was improved in the diabetic exercise group. Diabetic exercise group showed altered withdrawal latency to cold stimulus compared to the diabetic sedentary group. There was also significant change in the thermal hyperalgesia between control and diabetic sedentary group. Exercise improved thermal pain threshold in diabetic animals.

Conclusions

On the basis of biochemical analyses of the tissues, this study shows exercise reduced the up-regulation of proinflammatory cytokines, which may directly correlate with the pain in the diabetic animals. Overall, this research suggests that exercise may provide an alternate route of treatment for painful neuropathy in Type 1 diabetic and provide a more efficient way of management of pain.

The Psychiatric and Neurocognitive Manifestations of Sheehan’s Syndrome: A Case Report

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Introduction

Sheehan’s Syndrome is a state of hypopituitarism classically associated with postpartum necrosis of anterior pituitary occurring secondary to hypotension or hemorrhage. Although not the classic presentation for the illness, Sheehan’s Syndrome may present with psychiatric symptomatology such as psychosis, mood lability, and cognitive dysfunction.

Case Report

The patient was a 59 year-old Hispanic female with a recently di-
Agnosed history of bipolar disorder and dementia that was brought to the emergency room for evaluation of psychosis as well as mood and behavioral disturbances. While no history of previous psychiatric symptoms was initially reported, further questioning revealed a history of mood lability and cognitive disturbances secondary to severe postpartum hemorrhage during the birth of the patient’s second child. Glucocorticoid and thyroid supplementation was required to treat this condition. Additional information revealed a history of significant medication noncompliance. Sheehan’s syndrome was suspected. Laboratory findings were significant for hypokalemia, and low levels of TSH, free T3, free T4, and cortisol. Brain MRI findings were consistent with empty sella. Treatment with glucocorticoid and thyroid supplementation in addition to a small dose of antipsychotic medication resulted in resolution of psychiatric symptoms. Cognitive disturbances, however, remained.

Discussion
The case highlights neurocognitive and neuropsychiatric abnormalities associated with Sheehan’s Syndrome. While some acute psychiatric symptoms may improve with correction of the presenting endocrinopathies, cognitive dysfunction may persist. Further research examining the relationship between psychosis, dementia, mood disturbances, and chronic hypopituitarism in the context of Sheehan’s Syndrome is warranted.

A CRISPR-Cas9-based Screen for Human Genes Essential for West Nile Virus-induced Cell Death
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Introduction
West Nile virus (WNV) causes an acute neurological infection attended by massive neuronal cell death. However, the mechanism(s) behind the virus-induced cell death is poorly understood.

Materials and Methods
Using the Cas9/CRISPR tool, we conducted a genome wide screening of host genes involved in WNV infection induced cell death. We screened a library containing 77,406 sgRNAs targeting 20,121 genes, followed by a second screen with a sub-library.

Results
Among the genes identified, seven novel genes, EMC2, EMC3, SELH, DERL2, UBE2G2, UBE2J2, and HRDI, stood out as having the strongest phenotype, whose knockout conferred almost complete protection against WNV-induced cell death. Interestingly, knockout of these genes converted acute infections into chronic infections with persistent viral replication but no cell death.

Conclusions
These genes are part of a missing connection between WNV replication and the downstream cell death pathway(s). In addition, the fact that all of these genes belong to the ERAD pathway suggests that ERAD might be the important driver of WNV induced cell death.

Suicide Prevention: A Culturally Sensitive Approach to Determine Best Prevention Program for the El Paso Area
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Background
Suicide is one of the leading causes of death in adolescents and the rates are continuing to increase. Adolescent suicide is an extremely complex problem that is influenced by many different factors. Adolescent Hispanics are found to attempt suicide at a much higher rate than their white counterparts.

Methods
Phase 1 of this study included a retrospective review of suicide methods data from the Office of the Medical Examiner for the city of El Paso Texas that occurred in the last five years. Phase 2 of this study included a qualitative component including interviews with key experts in regards to: a) their experience of current suicide prevention programs in El Paso b) their thoughts on what type of culturally sensitive adolescent suicide prevention program would be most successful for this area.

Results
A total of 312 suicides were reported in El Paso County from 2009-2013. Adolescents suicides include 46 subjects mean age = 18.6 (SD = 2.23) range 15-21 years of age. A total of 10 people were interviewed, 6 female and 4 male. In answering the question, “What would be the ideal suicide prevention program you would support for this area?” 34 of 45 responses (76%) dealt with education. 47% supported an in home parent involvement educational prevention program.

Discussion
Adolescent suicide rate in El Paso is significantly lower than the National average, but still reported suicides occur in the Hispanic population. A culturally sensitive prevention program might be necessary for this area.

Inhibition of Breast Cancer Cell Growth and Sensitization to Chemotherapeutic Agents by the Carotenoid Lutein
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Introduction
Certain dietary carotenoids have been shown to have anti-cancer effects, but this phenomenon is not well studied in breast cancer. The present study tests the hypotheses that: (1) carotenoids sele-
tively inhibit cancer cell proliferation and/or induce apoptotic cell death, and (2) these carotenoids work additively or synergistically with chemotherapeutic agents (taxanes).

Materials and Methods
Breast cancer cell lines (MCF-7; MDA-MB-468 [triple negative]), an immortalized breast cell line (MCF-10A), and primary mammary epithelial cells (PMEC) were exposed to carotenoids (β-carotene, lycopene, lutein, astaxanthin) alone or with taxanes (paclitaxel or docetaxel). Cell proliferation was analyzed by MTT and EdU assays. Carotenoid-induced changes in cell cycle, apoptosis, intracellular ROS, gene expression, and cell signaling were also measured.

Results
Lutein and lycopene significantly inhibited breast cancer but not normal breast epithelial cell proliferation (threshold: <0.5 mM, similar to that induced by taxanes [paclitaxel and docetaxel]). The combination of taxane and lutein produced greater inhibition of cell proliferation than did either agent alone. Lutein treatment increased intracellular ROS, induced G0/G1 arrest, and altered expression of apoptosis-related genes. β-Carotene and astaxanthin had no effects on cancer cell growth.

Conclusions
Lutein and lycopene: (1) selectively inhibit cell growth in immortalized and breast cancer cells, independent of cell hormone receptor status, and (2) exhibit nearly equimolar growth inhibition to taxanes. These carotenoid-mediated effects appear to involve inducing cell cycle arrest, and increasing apoptosis. Nontoxic lutein and lycopene may be important in prevention or as adjuncts in breast cancer chemotherapy.

A Boy with Facial Edema and Hypertension

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Introduction
The most common cause of nephritis in the pediatric population is post streptococcal glomerulonephritis (PSGN). It typically follows an acute infectious process with an incubation period of one to three weeks. The clinical presentation of PSGN includes the onset of tea colored urine, hypertension (HTN), edema, and various degrees of renal dysfunction.

Materials and Methods
A 7-year-old boy presented to his pediatrician’s office with facial edema one week prior to hospital admission. The edema eventually worsened and spread from his face and abdomen over one week. One day prior to admission, the patient had sudden onset of tea-colored urine and hypertension so his pediatrician referred him to our facility. At presentation, the patient had a BP of 154/108. Review of systems revealed gross hematuria and subjective fever. Mild periocular edema and mild ascities were noted on physical exam.

Results
The laboratory results on admission were as follows: WBC, 20,000; hemoglobin, 12.3; platelets, 347; Sodium, 143; potassium, 3.7; CO2, 27; BUN, 15; creatinine, 0.44; and albumin, 3.4. The UA was positive for blood and 1+ protein with protein-creatinine ratio of 0.4. Complement C3 and C4 were low.

Conclusions
Treatment of PSGN is mainly supportive. Symptoms tend to resolve within one week but microscopic hematuria can remain present for 6 to 12 months. Patients with suspected PSGN need follow up C3 levels in 6 weeks. If the C3 level does not normalize by this time a kidney biopsy should be performed.

Characterization of Geriatric ED Patients by Sex

Susan Watts, PhD

Introduction
In general, geriatric (>65 yo) Emergency Department (ED) patients are more severely ill, have uncommon presentations, and greater occurrence of co-morbid disease than younger patients. Consequently many experience prolonged ED stays, require more laboratory/imaging tests, and larger proportion are admitted. However, little is known about differences in diagnosis and treatment of female vs male geriatric ED patients. Objective of this project was to identify some of those differences.

Materials and Methods
2010 National Hospital Ambulatory Medical Care Survey for Emergency Departments (NHAMCS-ED) was analyzed using appropriate weighting variables to derive population-based results.

Results
59% of geriatric ED patients were female and their odds of being admitted were slightly less than men’s (OR 0.91). Women’s odds were similar to men’s for having cerebrovascular disease or diabetes (OR’s 0.94 and 0.98, respectively) while odds of having CHF or requiring dialysis were less than men’s (OR’s 0.76 and 0.79, respectively). Women’s odds of having urinalysis were nearly double that of men (OR 1.89) while odds of other diagnostics were 14-30% higher (CBC, electrolytes, glucose, OR 1.14 to 1.30). Odds of bladder catheterization were ~40% greater (OR 1.39) and central line placement ~20% greater (OR 1.19). Odds of having CT imaging were similar but ultrasound exams in women were nearly three times higher (OR 2.87). Conversely, women’s odds of having CPR were 47% less than men’s (OR 0.53) and odds of dying in ED were 28% less (OR 0.72).

Conclusions
Differences in ED presentation, diagnosis, and treatment of geriatric women and men exist, and further study is needed.