A TIME OTHERWHERE

CHRISTINA
TODESCO-KELLY
&
JOHN
KELLY

A TIME OTHERWHERE

at Creative Brain Week
Exhibition Opening

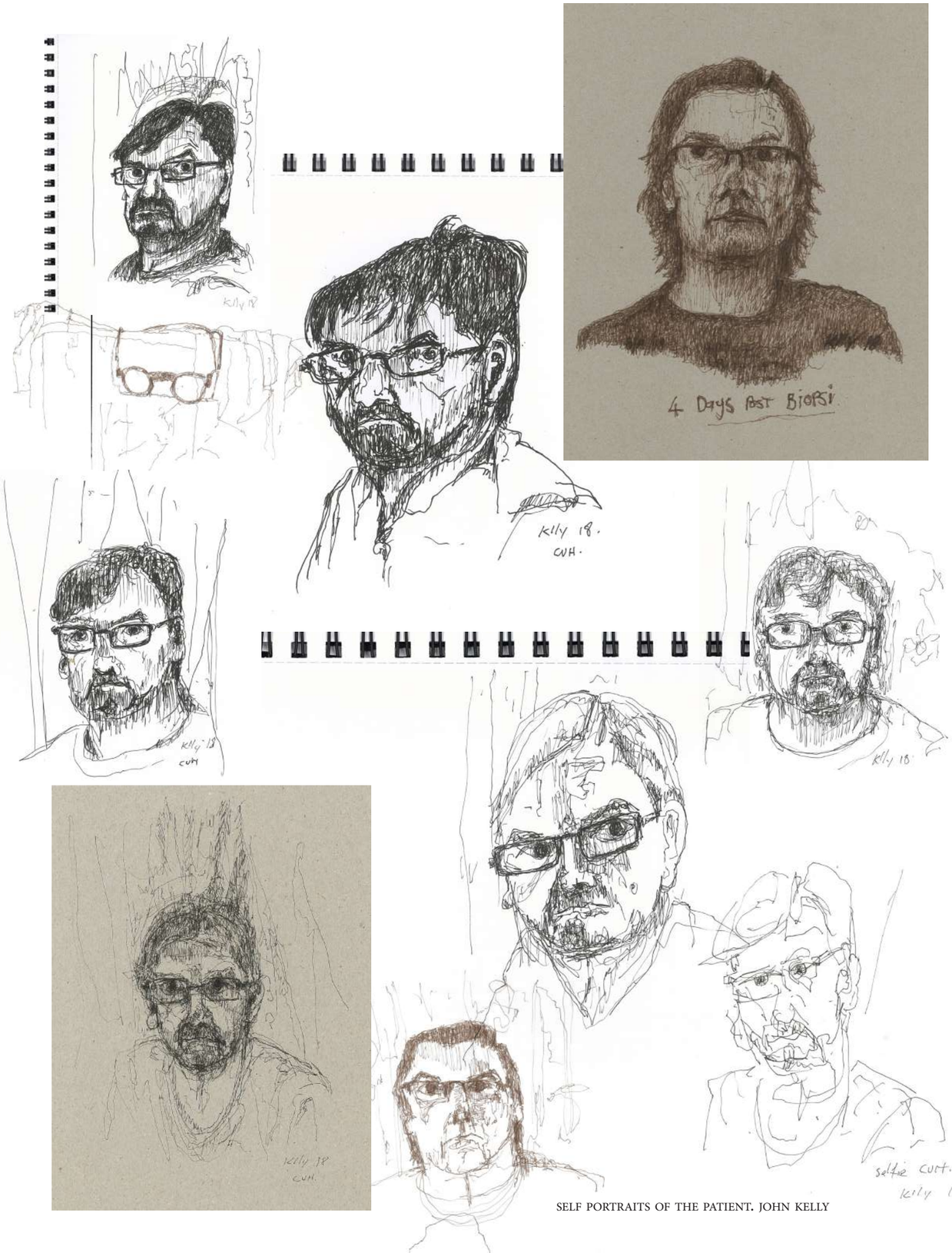
CHRISTINA
TODESCO-KELLY
&
JOHN
KELLY

With Dr Sarah Wrigley in conversation
with Professor Ian Robertson sharing
the backstory to the exhibition

TRINITY COLLEGE, DUBLIN

9th - 13th of June 2025

COVER IMAGE: PORTRAIT OF THE PATIENT. DRAWING AND PHOTOGRAPH BY CHRISTINA TODESCO KELLY.



SELF PORTRAITS OF THE PATIENT. JOHN KELLY

This is an acquittal report to Cork University Hospital following my 2018/2019 CUH Art Residency in which I wish to acknowledge their support and assistance in making this art possible.

John Kelly

My Cork University 'Art residency' was very much my own personal 'Chelsea Hotel' experience. Walking into its marijuana-scented lobby, I was stunned by the abundance of the most extravagant art pieces mixed together in a kind of "LSD–dictated" order hanging from the ceiling and on every wall, and I was overwhelmed by the thought that artists like Jackson Pollack, Christo (who stole the doorknobs of the hotel for an exhibition), Diego Rivera, Willem De Kooning, Robert Mapplethorpe, Cartier-Bresson, and many others, at some point, had lived here… Now, shots aside, drugs and rock'n'roll could not stay out of the Chelsea Hotel, so much so that Keith Richards, of the Rolling Stones, described the Hotel in one sentence: "You had to be a certified dealer to get a job as a bellboy."

The art within this catalogue was only made possible due to the work and expertise of the following doctors

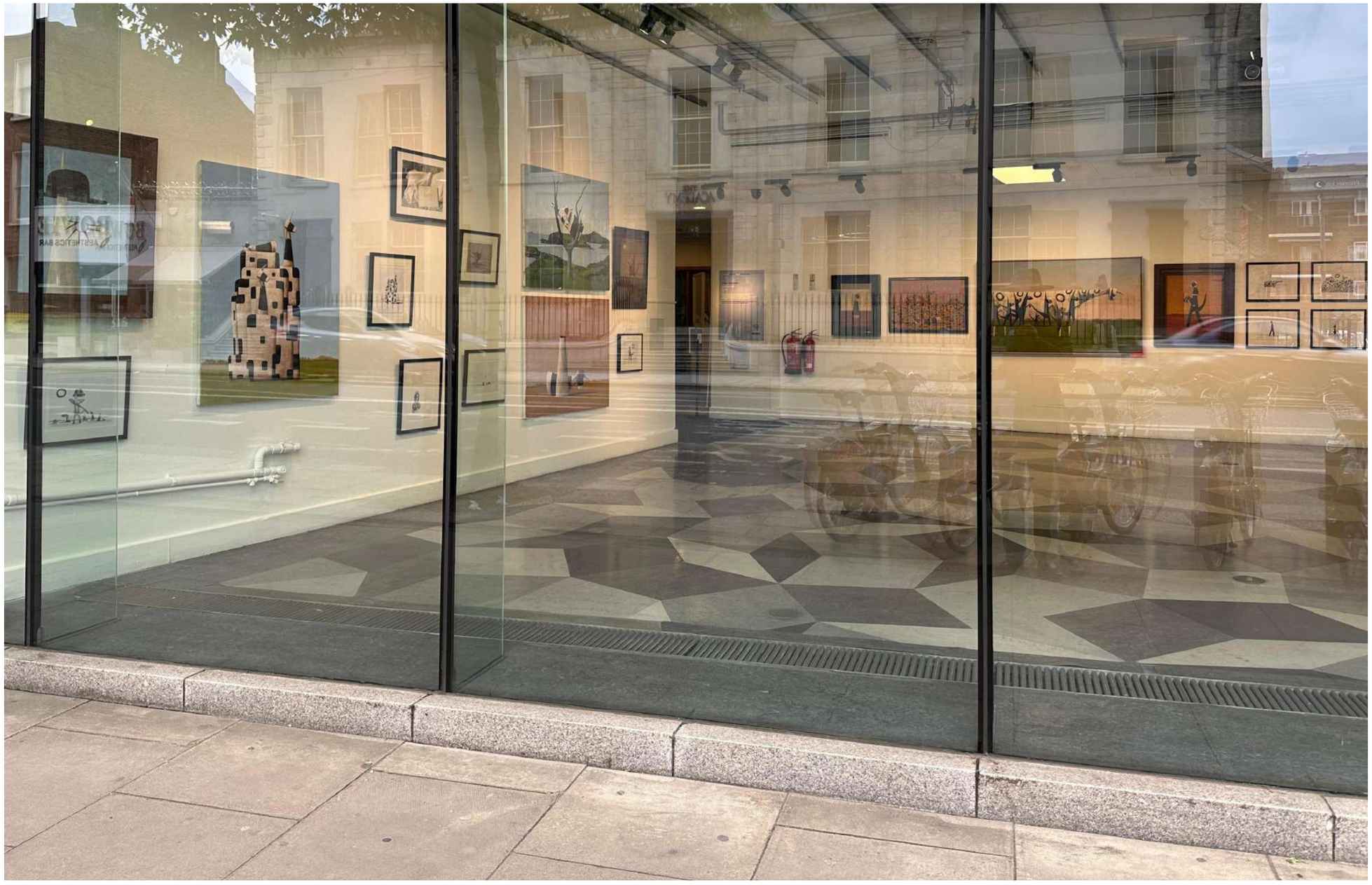
Dr. Ethna Phelan
Dr. Matt Dahm
Dr. Jason Van der Velde

and

The Nurses and staff at Cork University Hospital

With a very special dedication to

Dr. Stela Lefter



CREATIVE BRAIN WEEK EXHIBITION

On August 12th 2018, unexpectedly, I was admitted to a Cork University Hospital (CUH) art residency. I arrived by train. It was a frustrating trip, for it continually went around in circles, stopping and starting. Unlike most art residencies, I had a bed and staff were on call to wait on me. On the train I, unsuccessfully, tried to buy a pair of boots to cover the bare feet at the end of the bed. From this bed I noticed three people with their backs to me at a nearby desk. I sleep. I am awoken by rapid gun fire and cower; am I about to die? A large man with a scar on his neck hovers over me, with his soft voice he whispers, "You are safe John". I sleep. I am awoken by a man in green glasses with a beard. He asks, John do you know where you are? I don't know. I sleep. My machine wakes me, its beeping annoyingly consistent. The room becomes animated when the beep, behind the curtain, loses its consistency. The room is calm again as its beeping returns to normal. I begin to levitate and my view pixelates into blue. I Sleep. Is this a nightmare, have I had an accident? No, it is an alternative world, akin to Flann O'Brien's novel, The Third Policeman or Miloš Forman's One Flew Over the Cuckoo's Nest. It is a brief description of what turned from days to weeks and then months on 3A, the Neurology Ward in CUH.

In retrospect, it makes perfect sense; my brain interpreting its surroundings whilst in an ambulance, then a coma. The train? The bed being wheeled around the corridors for scans, X-rays and the changing of wards and rooms from the Intensive Care Unit to Room 11 on 3A, the high dependency room. The levitation was not an out of body experience but the bed being raised and lowered by a nurse; the blue pixels, the colour of the bed cover, seen through the eyes of a heavily drugged patient. The gunfire became a familiar sound in the MRI scans, the hallucinations the result of the plethora of drugs needed to bring me back from the abyss. At night, I drew strange looking self-portraits as the windows turned into reflective mirrors.

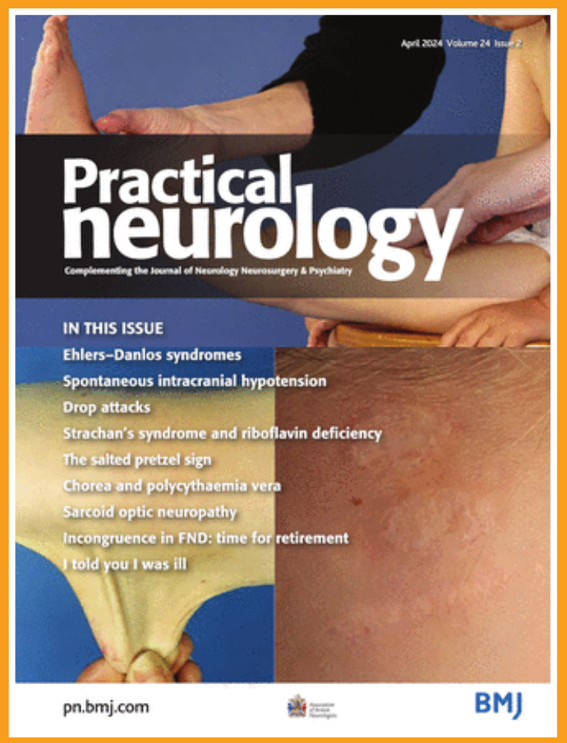
The long days that followed admission turned into weeks, then months. A brain biopsy, meeting Bob Geldof, two near death experiences. As the times passed, I moved down the corridor, room by room, each time getting closer to the doors that I was originally forbidden to pass. Upon leaving my CUH 'Art Residency' in late April 2019, I took home the sketchbooks in which I would draw day and night with a shaky hand to while away the boredom of being ill.

In late April 2019 I walked through those doors and now a small number of these sketches have become oil paintings and hang on the walls of Trinity College, Naughton Institute. Is this a dream or just another alternate reality? I will never be sure as this experience slides into my brain's memory bank.

"Somehow that broke this dream world he'd been living in, where the place was on fire and people were terrible. He then understood that some of what he saw was hallucinations. From then on he'd say to me "is this real? What's real now?"

www.independent.ie/entertainment/i-asked-is-john-going-to-die-and-the-consultant-said-probably/39450844.html

I told you I was ill



I told you I was ill

John Kelly,[1] Martin Maurice O'Donnell,[1] Sarah Wrigley,[1] Áine Merwick,[1,2] Stela Lefter[1,2]

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In August 2017, after receiving a phone call from my sister that my father was expected to die within days, I made an unexpected journey from my home in Ireland to Melbourne, Australia, to be with him. A long and daunting trip, on arrival, given my jetlag, I was put on the nightshift for his vigil. Partly instructed by his palliative care doctors, and partly by my father as he tapped on his cannula, unable to speak, I administered the painkillers as needed to make his journey easier. Ultimately, he passed peacefully, surrounded by family, as anyone would hope to, cared for and loved (figure 1). I expected to return to my life somewhat changed after this experience at least emotionally. However, shortly after his death and funeral, I had what I thought was an innocuous influenza-like illness, and instead things appeared to change utterly.

Over the following year, various problems arose including fatigue, 'brain fog', anxiety, severe headaches and tremors, along with some abrupt deteriorations that required short hospitalisations which I was told were 'silent migraines' and 'TIAs'. Having previously been a fit and active 53-year-old, exhibiting my works internationally, painting *en plein air* and publishing critical essays, as times passed, I eventually could no longer function, not just as an artist, but as a human. Various doctors of different creeds and training could not identify the cause of these symptoms, with a plethora of remedies and solutions suggested including amitriptyline (which only worsened matters), grief counselling, sea-swimming and seeing a psychologist. I was told more than once during this time that there was 'nothing wrong', and it was implied it was 'all in my head'. Things only progressed.

Finally, in August 2018, my illness truly revealed itself, culminating in my admission to Cork University Hospital, or as I refer to it, my illness-imposed 'art-residency'.

My recollection is that I travelled to my 'lodgings' by a train of some sort. It was a frustrating trip, for it continually went around in circles, stopping and starting. Acutely aware of my bare feet while lying down, I unsuccessfully tried to buy a pair of boots on the train from some staff. I noticed three people with their backs to me at a nearby desk. I slept.

I was awoken suddenly by rapid gunfire and cower. Am I about to die? A large man with a scar on his neck hovered over me and with a soft voice whispered, 'You are safe, John'. I slept.

I eventually arrive at my 'lodgings', at least for the time being. One of the staff members, a man in green glasses with a beard, woke me and asked, 'John, do you know where you are?'—I did not. I slept. A machine, however, continually woke me and kept me awake, its beeping annoyingly consistent. The staff would become animated, however, when the beeping lost

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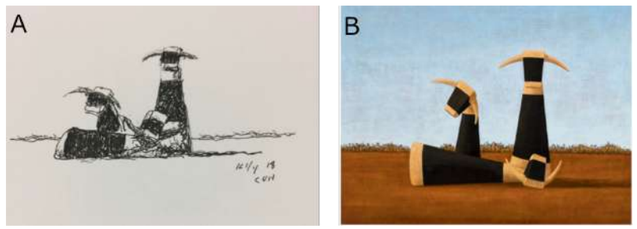

Figure 1 'The Lazarus Painting Conceived on My Death Bed' (2021) (B), along with the sketch from my time at Cork University Hospital (2018) that inspired it (A).

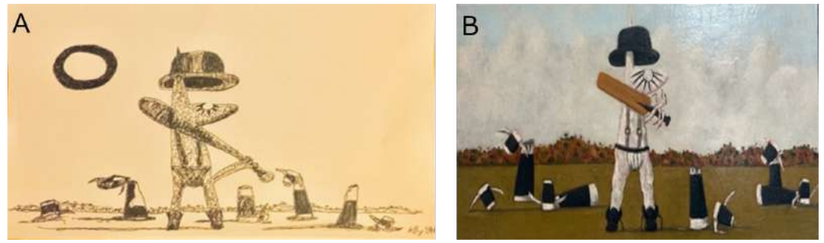

Figure 2 'Cow Massacre' (2019) (B) with the kangaroo Alex at large referencing Kubrick's Clockwork Orange, inspired by a sketch done during my time in hospital (A).

its consistency. The room would return to calm again when the beeping returned to normal. At one point, I levitated and my view pixelated into blue. I slept.

Is this a nightmare? Have I had an accident? It is a brief description of my perception of reality during my early days in the hospital. It felt like an alternative world, akin to Flann O'Brien's novel, The Third Policeman, or Stanley Kubrick's, One Flew Over the Cuckoo's Nest (figure 2). This sense of self and of the world seemed to be a result of my illness and the plethora of drugs needed to bring me back from the abyss. The train? The bed being wheeled around the corridors for scans, X-rays and the changing of wards and rooms from the intensive care unit to room 11 on 3A, the high dependency room. The gunfire and beeping were merely the rattling of the MRI machine and the monitors. The levitation was not an out of body experience but the bed was raised and lowered by a nurse; the blue pixels, the colour of the bed cover.

My wife's experience of the situation was undoubtedly different. A constant presence during this time, she saw me struggle with my reality early on, but also bore witness to my blossoming but fragile recovery. Several weeks into my residency, I was in 3A with my wife when I thought I had heard voices from behind the curtain of the next bed. I thought they were being critical and threatening to us. She assured me it was an elderly couple, with a very sick middle-aged daughter, but I did not believe her. She got me out of bed, and she wheeled me around with the excuse of going to the toilet, and I looked in and there lay the true reality for me to see. She tells me I asked 'Is this real? What's real now?'. From thereon, by my side, she helped me navigate my reintroduction to the real world and became an arbitrator of sorts of what was real, and what was not, until I once again could by myself (figure 3).

I could appreciate my own improvement with time artistically also. At night I began to draw again, initially strange looking self-portraits with the windows serving as reflective mirrors (figure 4). I then drew day and night with a shaky hand to while away the boredom of illness, gradually noting the recovery personally and in my art (figures 1–3).

Test after test, up to and including a brain biopsy, led to a diagnosis of primary CNS vasculitis, and from there, a gradual but precarious road to recovery with powerful drugs, themselves not without consequences. As time passed, I moved down the corridor, room by room, each time getting closer to the doors that I was originally forbidden to pass. In late April 2019, I walked through the same doors I entered changed and inspired as a person somewhat but also as an artist, inspired and awed by what had happened.

COMMENTARY FROM HIS TREATING TEAM

Medicine is a specialty increasingly drawn to objectifying the subjective, attributing signs and symptoms to the manifestations of illness, quantifying the severity of illness through laboratory tests and imaging, and trying to scale the functional outcomes. The experience

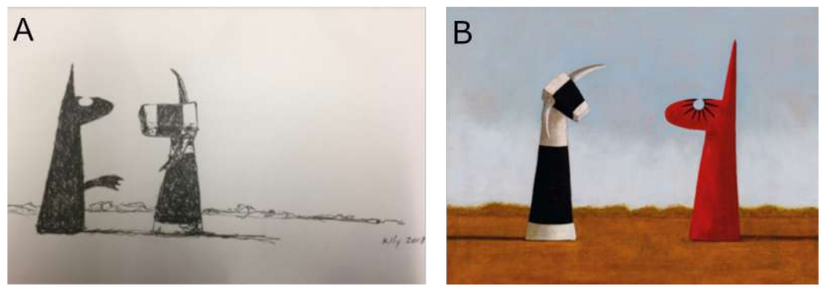

Figure 3 'Incorrect Shadows (A Conversation)' (2020) (B), where the old world and new world come face to face with each other, inspired by a sketch done during my time in hospital (A).

Figure 4 First night self-portrait as seen in the reflective window in room 11, on ward 3A in Cork University Hospital soon after coming out of the coma.

of illness, however, for individual patients is not quantifiable nor standard, and sometimes in the push to objectify, we can lose sight of this and the humanity of an individual situation.

John's ability to communicate and portray visually his tribulations so viscerally was something we noted post his illness at Cork University Hospital and in the outpatient clinic. As such, we encouraged John to write this piece as we felt other healthcare professionals could also learn and be inspired by his story.

John's journey to a diagnosis of primary CNS vasculitis shows the impact diagnostic uncertainty can have on someone between inappropriate investigations, referrals and treatments, all the while, being taxed with the human cost of an illness, with the condition affecting his personal and work life and interfering with his sense of self. His otherworldly experience in hospital meanwhile is a direct insight into the experience of impaired consciousness and encephalopathy, something we may find easy to diagnose but difficult to explain to patients and families. Finally, while John's story of recovery is inspiring alone, his works that illustrate the piece add another dimension and allow us to visualise recovery in the arts, something we unfortunately do not get the opportunity to see often.

Twitter Martin Maurice O'Donnell @martinmodonnell

Contributors JK, MMO'D, SW, ÁM and SL conceptualised the paper, with JK writing the initial patient contribution and MMO'D, SW, ÁM and SL writing the treating team contribution, with all authors contributing to editing and revisions. All are acknowledged as authors of this paper. All authors approved the final draft for submission.

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Ethics approval This study involves human participants and patient consent was obtained for publication from JK, with JKa also being an active contributor to the work and an acknowledged author.

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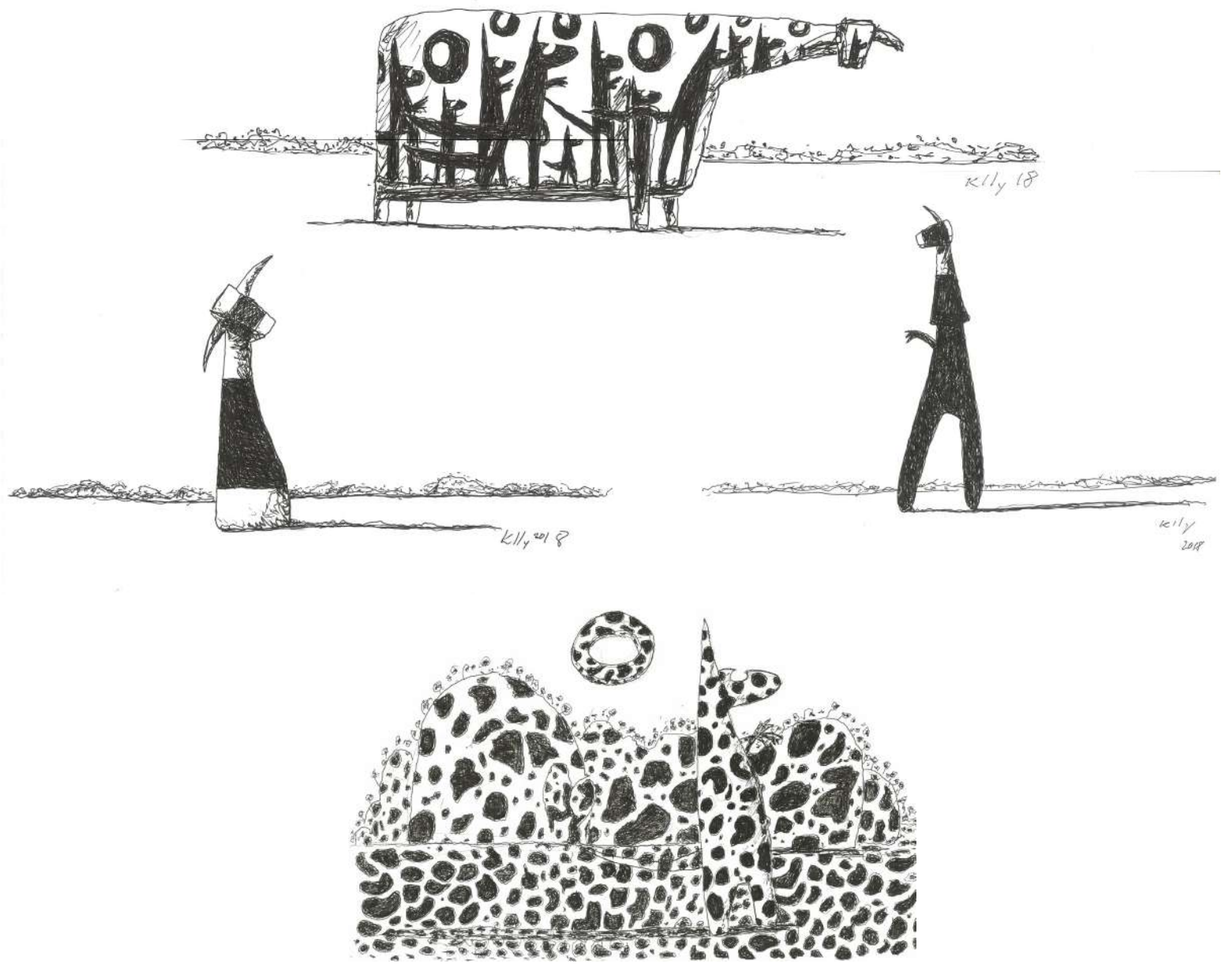
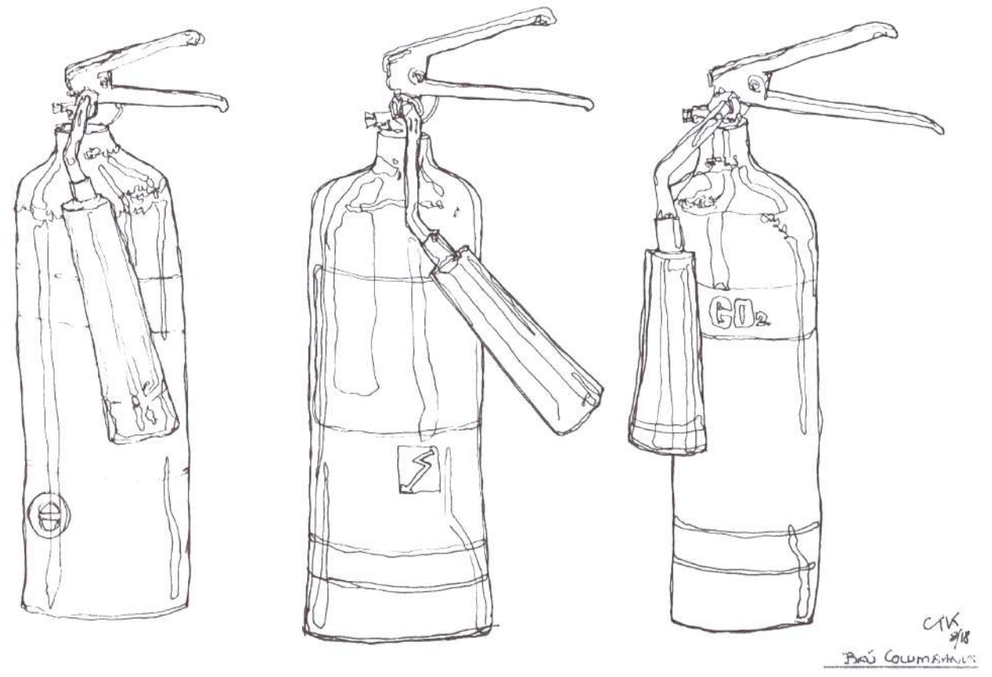
Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study. No data are available.





CHRISTINA TODESCO-KELLY'S STILL LIFE DRAWING CREATED IN BRÚ COLUMBANUS

CHRISTINA TODESCO-KELLY'S LIFE DRAWING OF THE PATIENT CREATED IN CUH

CHRISTINA TODESCO-KELLY'S STILL LIFE DRAWING CREATED IN CUH

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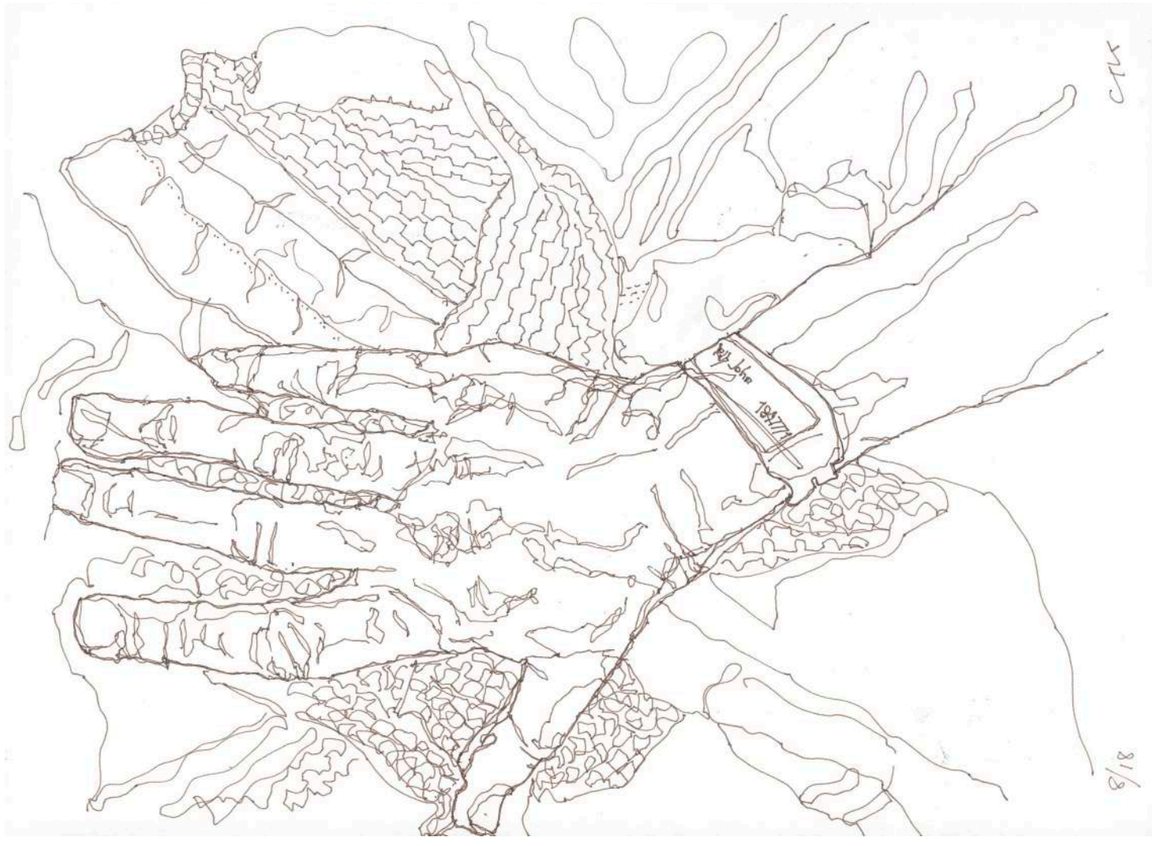
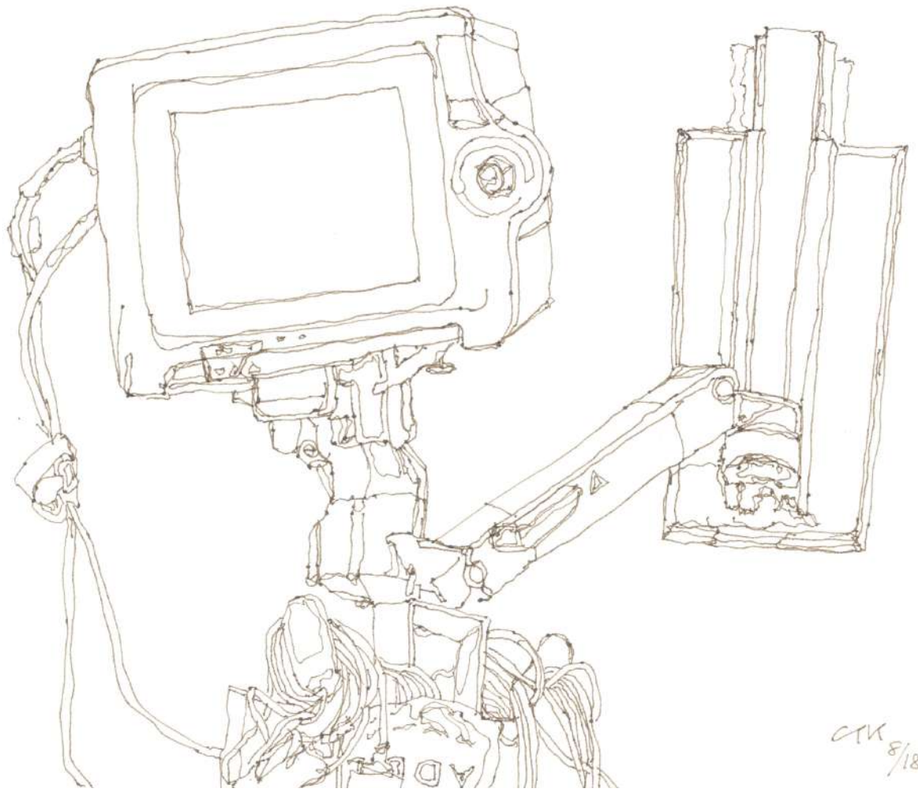
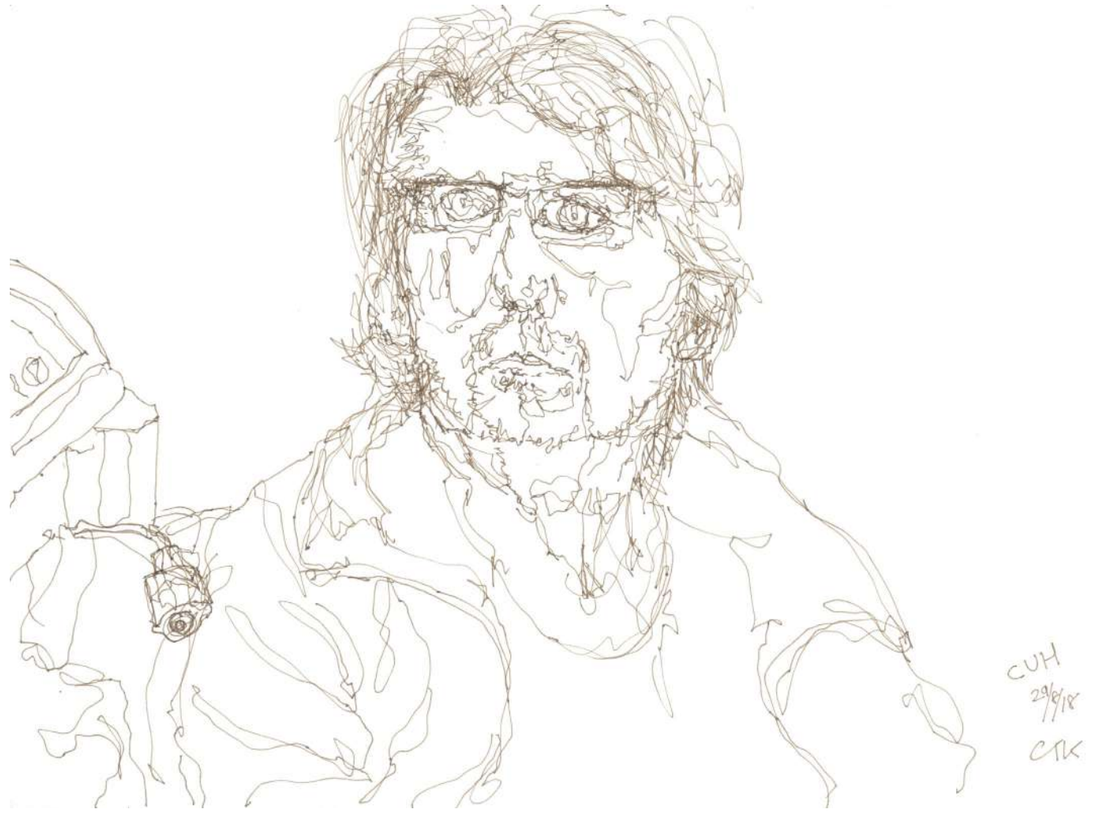


CHRISTINA TODESCO-KELLY'S LIFE DRAWING OF THE PATIENT CREATED IN CUH

CHRISTINA TODESCO-KELLY'S LIFE DRAWINGS OF THE PATIENT CREATED IN CUH

CHRISTINA TODESCO-KELLY'S STILL LIFE DRAWING CREATED IN CUH



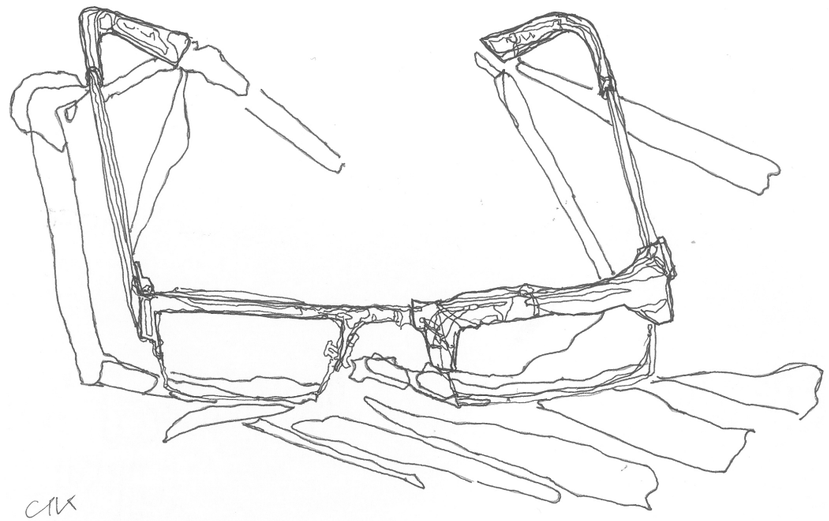


CHRISTINA TODESCO-KELLY'S LIFE DRAWING OF THE PATIENT CREATED IN CUH

CHRISTINA TODESCO-KELLY'S LIFE DRAWING OF THE PATIENT CREATED IN CUH

John's Slippers (CUH)

CTK 8/18



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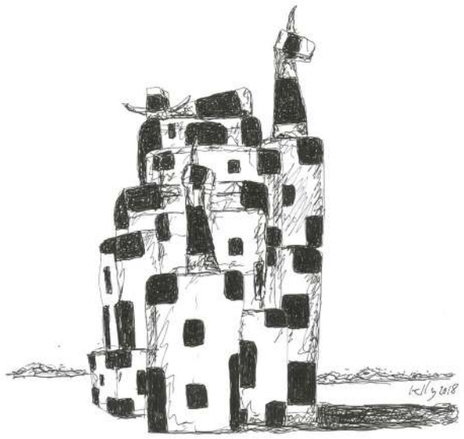

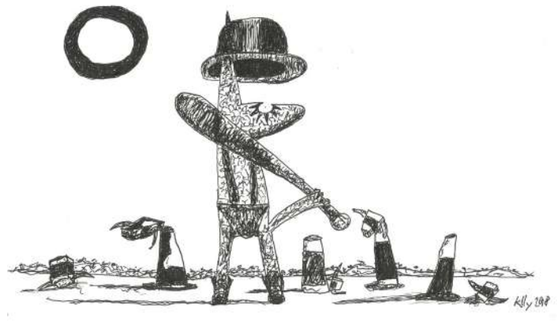

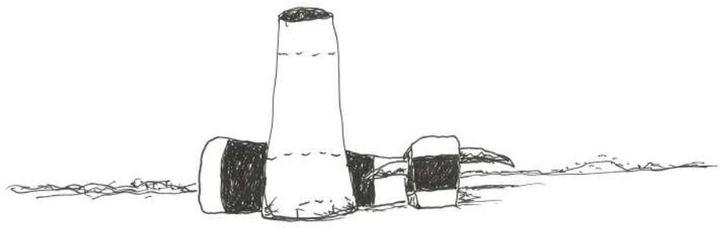

Treatment-Resistant Small Vessel Primary Angiitis of the Central Nervous System

This case illustrates challenges encountered in the diagnosis and management of small-vessel primary angiitis of the central nervous system.

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Case Presentation

KH-C, age early 50s with no known medical history, was admitted to the hospital emergently with new-onset status epilepticus. Glasgow Coma Scale score on arrival was 3/15. Immediate intubation, transfer to intensive care, and treatment with intravenous (IV) midazolam, phenytoin, and levetiracetam were performed. A fever (38.5° C) was documented. Cerebrospinal fluid (CSF) revealed lymphocytic pleocytosis (white cell count 18/mm^3), elevated protein level (1640 mg/L), and normal glucose level (5.4 mmol/L), prompting empiric treatment for infectious meningoencephalitis. CSF opening pressure was not assessed.

Collateral history obtained from the family revealed that KH-C had experienced progressive neuropsychiatric decline over almost 1 year. Twelve months previously, in August, KH-C had contracted a flu-like illness while in Australia, which had resolved within 2 weeks. Two months later, on return to Ireland in October, KH-C's partner had noticed subtle personality change including new-onset anxiety and irritability. The following month, KH-C had a 30-second episode of dysarthria that was diagnosed as a transient ischemic attack on the basis of normal MRI results. KH-C had consulted numerous neurologists and had been given various diagnoses including transient ischemic attack and migraine. KH-C had commenced amitriptyline for migraine prophylaxis, which was later stopped following a 30-minute episode of drowsiness and disorientation. In December, 2 months after the personality changes had first been noted, KH-C had experienced bouts of fever with confusion and visual hallucinations, which resolved after 2 weeks. Over the next 6 months, KH-C had complained of generalized weakness, paresthesia, and headaches, and had repeatedly presented to the general practitioner for antibiotics. KH-C had difficulty focusing on tasks and had developed a postural hand tremor. Further presentations to physicians had led to a diagnosis of generalized anxiety with panic attacks. By April, KH-C had developed monthly stereotyped episodes of dysarthria and perioral numbness. Finally, 10 months after returning from Australia, KH-C had a further episode of dysarthria that developed into a bilateral tonic-clonic seizure, leading to this hospital admission.

TABLE 1. SUMMARY OF INVESTIGATIONS YIELDING NEGATIVE RESULTS

Infection screening	• Blood, CSF, and urine bacterial and fungal cultures • CSF PCR for HSV-1 and HSV-2, VZV, EBV, CMV, enteroviruses, and JCV • Serology for HIV, hepatitis B and C, syphilis, Lyme disease, cryptococcus, histoplasmosis, and coccidioidomycosis
Vasculitis screening (serum)	• ANA and anti-dsDNA • ENA, anti-Ro, and anti-La • c-ANCA and p-ANCA • Cryoglobulins
Granulomatous screening (serum)	Serum ACE and IgG4
CNS autoimmune screening (CSF and serum)	• NMDA-R, LGI1, Caspr2, GABA-A, GABA-B, AMPAR, DPPX, GAD65, Glycine-R, and GFAP • AQP4 and MOG antibodies • Paraneoplastic antibodies (Hu, Ro, La, CV2, Tr, Ma1, Ma2, and amphiphysin)
Malignancy screening	• CT of the thorax, abdomen, and pelvis • Testicular ultrasound • 18F-FDG whole-body PET–CT • CSF cytology and flow cytometry

Abbreviations: ACE, angiotensin-converting enzyme; AMPAR, AMPA glutamate receptor; ANA, antinuclear antibodies; AQP4, aquaporin-4; c-ANCA, cytoplasmic antineutrophil cytoplasmic antibodies; Caspr2, contactin-associated protein-like 2; CMV, cytomegalovirus; CNS, central nervous system; CSF, cerebrospinal fluid; DPPX, dipeptidyl-peptidase-like protein 6; dsDNA, double-stranded DNA; EBV, Epstein-Barr virus; ENA, extractable nuclear antigen; FDG, fluorodeoxyglucose; GABA, gamma-aminobutyric acid; GAD65, glutamic acid decarboxylase 65; GFAP, glial fibrillary acidic protein; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IgG4, immunoglobulin G4; JCV, John Cunningham virus; LGI1, leucine-rich glioma-inactivated 1; MOG, myelin oligodendrocyte glycoprotein; NMDA-R, NMDA receptor; p-ANCA, perinuclear antineutrophil cytoplasmic antibodies; PCR, polymerase chain reaction; PET, positron emission tomography; VZV, varicella-zoster virus.

Diagnostic Process

Initial laboratory testing demonstrated neutrophilia (27 x 10^9/L) but normal erythrocyte sedimentation rate and C-reactive protein level. CSF bacterial and fungal culture, and polymerase chain reaction for herpes simplex virus (HSV)–1 and HSV-2, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, and enterovirus, had negative results (Table 1). There were faint unmatched CSF oligoclonal bands. EEG demonstrated diffuse slow-wave activity without evidence of ongoing seizure activity. Brain MRI showed multiple subcortical fluid-attenuated inversion recovery (FLAIR) hyperintensities in the frontal, parietal, and temporal lobes bilaterally, and scattered subcortical microhemorrhages on susceptibility-weighted imaging (Figure 1). There was no restricted diffusion or gadolinium enhancement. Spinal cord MRI results were normal. Although there was no enhancement, the brain imaging results were consistent with a diffuse neuroinflammatory process and, given the cortical microhemorrhages, a diagnosis of cerebral amyloid angiopathy–related inflammation (CAA-ri) was considered.

On day 2 of admission, after initial infection screens had negative results, KH-C received empiric treatment for a central nervous system (CNS) autoimmune or inflammatory process, which included a single course of IV immunoglobulin (0.4 g/kg/d for 5 days) and IV methylprednisolone (1 g/d for 5 days) followed by oral prednisolone (60 mg/d). KH-C improved quickly and was transferred to a standard ward within 4 days. Seizures ceased, and KH-C's year-long alteration in personality began to improve.

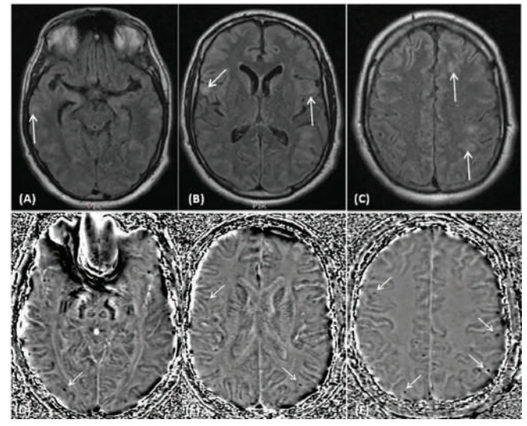

Figure 1. Brain MRI on admission demonstrated diffuse subcortical fluid-attenuated inversion recovery (FLAIR) hyperintensities throughout the frontal, parietal, and temporal lobes bilaterally (A–C). Phase susceptibility-weighted imaging sequences demonstrated scattered subcortical microhemorrhages (D–F). The arrows point to examples of subcortical FLAIR hyperintensities and phase microhemorrhages.

KH-C underwent a comprehensive evaluation, including screening for infectious, inflammatory, autoimmune, and paraneoplastic causes, all of which had negative results (Table 1). CSF flow cytometry showed a predominant T-cell

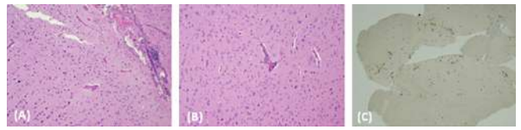

Figure 2. Representative slides from the brain biopsy. Hematoxylin & eosin histochemical staining showed cortical and leptomeningeal tissue with perivascular lymphocytic inflammation and mild lipohyalinosis. No fibrinoid necrosis, amyloid, granulomas, or infectious agents were identified (immunohistochemistry and histochemistry not shown) (A, B). CD3 immunohistochemistry highlighted scattered T-cell lymphocytes in a predominantly perivascular distribution (C).

lymphocytic population without B-cell monoclonality. Glial fibrillary acidic protein (GFAP) antibody testing was unavailable at that time; however, there were no imaging features suggestive of GFAP astrocytopathy.[1] Catheter-based cerebral angiography demonstrated normal intracranial vasculature.

Three weeks after commencing steroid therapy, KH-C had an untargeted open right frontal lobe biopsy (Figure 2), as no inflammatory lesions were surgically accessible outside of eloquent cortex. Cortex, white matter, and leptomeningeal tissue were sampled. Histochemical staining with hematoxylin & eosin, as well as CD3, CD20, and CD68 immunohistochemistry, were performed (Figure 2) and revealed foci of perivascular predominantly T-lymphocytic inflammation without vessel wall infiltration. Granulomas were absent. There was perivascular clustering of macrophages, microglial activation, and astroglial reaction, suggesting microscopic ischemia. However, Verhoeff-van Gieson and Martius Scarlet Blue stains did not show vessel wall destruction or fibrin deposition to support a necrotizing vasculitis. β-amyloid antibody testing did not identify amyloid angiopathy. Periodic acid-Schiff and Ziehl-Neelsen stains for fungi and acid-fast bacilli, respectively, had negative results. Immunohistochemistry for *Toxoplasma gondii*, HSV-1, HSV-2, and human polyomavirus 2 (JC virus) had negative results. Myelin basic protein immunohistochemistry did not show demyelination. Overall, the biopsy features supported an inflammatory process that could be seen in a variety of conditions including a treated vasculitis or autoimmune process.

Given the clinical history and the biopsy findings of perivascular inflammatory cell infiltration and microscopic ischaemia in the absence of an infectious agent or causative antibody, a multidisciplinary meeting came to a consensus diagnosis of small-vessel primary angiitis of the CNS (SV-PACNS).

Case Resolution

KH-C continued to improve on oral steroids and, once initiated on a regimen of monthly IV pulse cyclophosphamide, was discharged home. However, KH-C presented 6 weeks later with headaches and recurrence of focal seizures. Repeat MRI showed new subcortical FLAIR hyperintensities (Figure 3, E–H). By this time, KH-C was on prednisolone 20 mg and had received 2 courses of 1 g cyclophosphamide. Following negative CSF bacterial and fungal culture and viral polymerase chain reaction (PCR) testing, KH-C received IV methylprednisolone 1 g/d for 5 days followed by oral prednisolone 40 mg/d.

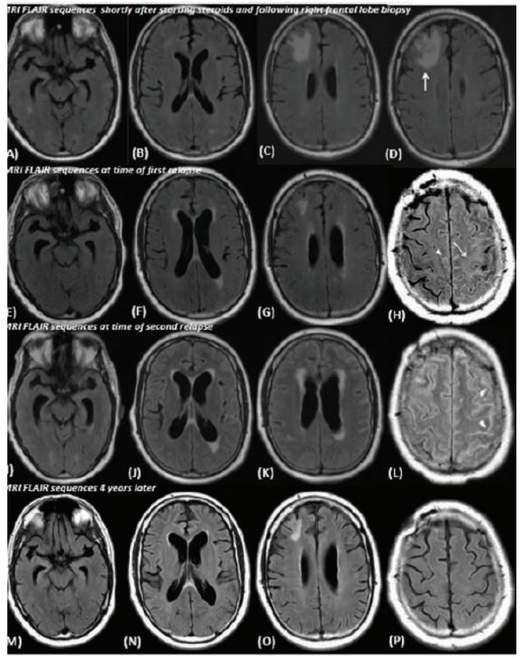

Figure 3. Serial MRI fluid-attenuated inversion recovery (FLAIR) images taken shortly after the right frontal lobe brain biopsy (A–D), at the time of the second relapse 3 months later (E–H), and at the time of the third relapse 1 month after that (I–L) demonstrated new and progressive ventriculomegaly with surrounding FLAIR signal changes. There is increased FLAIR high signal in the subcortical white matter (arrow, H) and in the subarachnoid space (arrowheads, H and L) despite treatment with intravenous cyclophosphamide. The right frontal lobe signal change was secondary to the biopsy (arrow, D). Long-term resolution of periventricular, subcortical, and sulcal FLAIR signal abnormality was noted 4 years after the start of rituximab treatment (M–P).

KH-C's condition improved clinically and radiologically. However, KH-C presented again 8 weeks later (after 2 further cycles of cyclophosphamide) with general malaise and fever. Serial MRIs demonstrated progressive ventriculomegaly with surrounding FLAIR signal changes and increased FLAIR high signal in the subcortical white matter and subarachnoid space (Figure 3, E–L).

Given the stepwise deterioration despite immunosuppression accompanied by recurrence of fever and inflammatory CSF changes, the diagnosis was queried by the attending consultant neurologist, and an extensive search for an infectious cause was repeated. This included repeat CSF culture and 16S/18S rRNA sequencing for bacterial or fungal infections (performed at University of Warwick, Coventry, UK). The first sample was positive for *Coniochaeta* sp; however, repeat sample had negative results. In total, CSF was sampled 6 times for infectious agents over the course of KH-C's illness with consistently negative results. KH-C was treated empirically with antifungal agents (IV amphotericin and flucytosine followed by oral fluconazole) but continued to deteriorate.

Given the lack of an identifiable infective agent and following consultation with international experts in PACNS, this case was considered SV-PACNS refractory to conventional immunosuppression. The consensus was to proceed with further immunosuppression with high-dose steroids and rituximab (375 mg/m^2) once weekly for 4 weeks to be repeated 6-monthly thereafter. On this regimen, KH-C demonstrated a sustained clinical and radiologic improvement. Immunosuppression was weaned after 2 years, and KH-C has remained in remission since that time (Figure 3, M–P).

Discussion

PACNS is a rare condition characterized by inflammation of the blood vessels of the brain and spinal cord. The estimated prevalence is 2.4/1,000,000 person-years.[2] Clinical symptoms are variable and nonspecific, and both pathognomonic clinical signs and a characteristic clinical course are lacking. PACNS may present acutely or subacutely but more commonly has an insidious presentation with a chronically progressive or fluctuating course that may delay diagnosis, as occurred in our patient. The most common presenting symptoms are headache (58%) and cognitive dysfunction (54%), followed by focal neurologic deficit or stroke (43%) and seizures (20%).[3] Myelopathy can occur with spinal cord involvement (5%).[4] Systemic manifestations such as fever, fatigue, anorexia, and weight loss are present in <10% of cases.[2] This clinical heterogeneity is partly attributable to the size of the arteries involved. People with medium or large-vessel PACNS are more likely to present with headaches and focal neurologic deficits, whereas a greater proportion of people with SV-PACNS present with cognitive impairment, encephalopathy, and seizures.[5]

No laboratory or imaging investigations are available to reliably confirm a diagnosis of PACNS. Routine bloodwork including acute phase reactants (ie, erythrocyte sedimentation rate and C-reactive protein) generally has normal results, and brain MRI findings are nonspecific, ranging from acute focal or multifocal cerebral infarctions to T2/FLAIR hyperintensities, to parenchymal or meningeal gadolinium enhancement, to leptomeningeal enhancement or, least commonly, to intracerebral hemorrhage.[6] The incidence of cortical microhemorrhages in SV-PACNS, as observed in our case, is increasingly recognized.[7] CSF usually shows lymphocytic pleocytosis and elevated protein level. The differential diagnosis is lengthy, necessitating extensive evaluation for CNS infectious, autoimmune, rheumatologic, and granulomatous diseases, systemic vasculitis, and malignancy, as shown in this case.

Infectious vasculitis may be caused by direct endothelial invasion and vessel wall destruction by the pathogen or by an immune response to the pathogen[8] and was important to rule out in our case given the history of an initial infective illness in the context of foreign travel. Infectious vasculitis can be seen in the context of bacterial or tuberculous meningitis, neurosyphilis, or neuroborreliosis as well as viral and fungal infections, including varicella-zoster virus, HIV, aspergillosis, and cryptococcus.[8] However, an infective agent was never identified in our patient.

Hemophagocytic lymphohistiocytosis (HLH) is a rare hyperinflammatory syndrome characterized by impaired CD8+ cytotoxic T cell and natural killer cell[9] function that may be triggered by infection[10] and rarely is restricted to the CNS, thereby mimicking what is seen in those with PACNS. Neither the pathology specimens nor CSF cytology showed evidence of hemophagocytosis to suggest HLH.[10] However, further studies to explore the possibility of HLH, such as natural killer cell activity or soluble CD25 levels, should be considered.[10]

The diagnostic criteria for PACNS[11,12] (Table 2) require supportive evidence from either a cerebral angiogram or brain biopsy. However, these requisite tests have their pitfalls in the diagnosis of PACNS. Angiographic findings include multifocal segmental arterial stenoses with intervening dilation (ie, beading), occlusions, and collateralization,[13] but these features are not specific to PACNS and are seen in noninflammatory vasculopathies such as intracranial atherosclerosis, reversible cerebral vasoconstriction syndrome, and moyamoya vasculopathy, and as reactive changes after subarachnoid hemorrhage or irradiation. MRI with vessel wall imaging can provide a suggestive arterial wall enhancement pattern that can be helpful in differentiating PACNS from some of these conditions. However, angiography results are typically normal in cases of SV-PACNS, where the involved arteries are <500 μm in diameter,[14] and overall angiography has positive results in only 15% to 43% of cases of biopsy-proven PACNS.[13,15,16]

Brain biopsy remains the gold standard for diagnosis of definite PACNS and characteristically shows a transmural

TABLE 2. DIAGNOSTIC CRITERIA FOR PRIMARY CENTRAL NERVOUS SYSTEM VASCULITIS
Diagnostic criteria[11]
1. Presence of an unexplained neurologic deficit after thorough clinical and laboratory evaluation
2. Documentation by cerebral angiography or tissue examination of an arteritic process within the central nervous system
3. No evidence of a systemic vasculitide or any other condition to which the angiographic or pathologic features could be secondary
Amended diagnostic criteria[12]
1. Definite PCNSV: confirmation of vasculitis on analysis of a tissue biopsy specimen
2. Probable PCNSV: in the absence of tissue confirmation, high-probability findings on an angiogram with abnormal findings on MRI and a cerebrospinal fluid profile consistent with PCNSV
Abbreviation: PCNSV, primary central nervous system vasculitis.

inflammatory cell infiltrate and vessel wall destruction. There are 3 histologic patterns: granulomatous, lymphocytic, and necrotizing. Granulomatous vasculitis is associated with vascular amyloid-β (Aβ) deposition in 50% of cases,[2] and is diagnosed as Aβ-associated angiitis, a condition that exists on a spectrum with CAA-ri. CAA-ri is characterized by perivascular inflammation resulting from amyloid-β deposition without vessel wall destruction. Aβ-associated angiitis and CAA-ri, common differential diagnoses for PACNS, were not detected on biopsy in our patient given the lack of vascular amyloid-β deposition.

Brain biopsy has limitations; given the segmental distribution of vascular inflammation, the sensitivity of brain biopsy is only 53% to 76% due to sampling error.[8,14,17] Furthermore, patients have sometimes already received empiric steroid therapy by the time they undergo brain biopsy, which can compromise the findings, as probably occurred in our patient. As a result of these issues, 18% to 40% of cases included in studies of PACNS lack definitive biopsy findings.[16,18]

When possible, clinicians should delay steroid therapy until biopsy results are available, although this is not always feasible in cases such as ours, where the patient presented in extremis. The diagnostic yield of brain biopsy is greatly improved by targeting a radiologically abnormal region—particularly a gadolinium-enhancing parenchymal or leptomeningeal lesion.[17,19] However, this is not always possible, as in this case, where there was no surgically accessible lesion at the time of biopsy, and reliance on pathologic findings from untargeted nondominant frontal lobe biopsies is not uncommon.[17] Open biopsy is preferable to stereotactic methods in a diffuse process like PACNS to maximize the chance of sampling an abnormality and to preserve the microscopic anatomy so that a more descriptive reporting of the findings is possible.

Given the lack of clear clinical descriptors and the difficulties inherent in the confirmatory diagnostic tests, cases of treatment-resistant PACNS represent a particular source of concern for the treating neurologist. There may be lingering diagnostic doubt, which may come to the fore in instances where the patient demonstrates a suboptimal response to treatment. The most common therapeutic strategy for PACNS is high-dose glucocorticoid treatment followed by prolonged immunosuppression with cyclophosphamide, mycophenolate mofetil, or azathioprine. However, no randomized controlled clinical trials examining the optimal treatment strategy for PACNS have been undertaken.[8] Our patient relapsed while on treatment with maintenance cyclophosphamide when the prednisolone dose was reduced to 20 mg. A thorough search for CNS infections was conducted, which delayed reinstatement of full-dose immunosuppression. Consultation with international experts was undertaken to ensure confidence in the diagnosis of PACNS, and based on recent evidence in treatment-resistant PACNS, KH-C was commenced on rituximab.[18] The patient made a profound recovery and remains in clinical and radiologic remission, as illustrated by follow-up imaging at 4 years after the start of rituximab treatment. KH-C's case is now one of many supporting the use of rituximab in treatment-resistant PACNS.[20]

This case illustrates the challenges encountered in the diagnosis and management of SV-PACNS. Given the limitations of the primary diagnostic tests and the lack of prospective clinical trials to provide an evidence base for treatment decisions, this case emphasizes the need for clinicians to be supported by a multidisciplinary team comprising clinical neurologists, neuroradiologists, and neuropathologists, as well as input from a clinical team with relevant expertise in PACNS, to provide a consensus diagnosis and treatment approach. The delay in diagnosis due to indolent presentation observed in this case highlights the need for clinicians to have a high clinical suspicion for SV-PACNS in progressive neuropsychiatric syndromes. ■

1. Flanagan E, Hinson S, Lennon V, et al. Glial fibrillary acidic protein immunoglobulin G as biomarker of autoimmune astrocytopathy: analysis of 102 patients. Ann Neurol. 2017;81(2):298-309. doi:10.1002/ana.24881
2. Salvarani C, Brown RD Jr, Hunder G. Adult primary central nervous system vasculitis. Lancet. 2012;380(9843):767-777. doi:10.1016/S0140-6736(12)60069-5
3. Salvarani C, Brown RD Jr, Christianson T, et al. Long-term remission, relapses and maintenance therapy in adult primary central nervous system vasculitis: a single-center 35-year experience. Autoimmun Rev. 2020;19(4):102497. doi:10.1016/j.autrev.2020.102497
4. Salvarini C, Brown RD Jr, Calamia K, et al. Primary CNS vasculitis with spinal cord involvement. Neurology. 2008;70(24 Pt 2):2394-2400. doi:10.1212/01.wnl.0000314687.69681.24
5. De Boysson H, Boulouis G, Aouba A, et al. Adult primary angiitis of the central nervous system: isolated small-vessel vasculitis represents distinct disease pattern. Rheumatology. 2017;56(3):439-444. doi:10.1093/rheumatology/kew434
6. Salvarani C, Brown RD Jr, Christianson C, et al. An update of the Mayo Clinic cohort of patients with adult primary central nervous system vasculitis: description of 163 patients. Medicine (Baltimore). 2015;94(21):e738. doi:10.1097/MD.0000000000000738
7. Guo A, Zhang Z, Dong GE, et al. Cortical microhemorrhage presentation of small vessel primary angiitis of the central nervous system. Ann Neurol. 2024;96(1):194-203. doi:10.1002/ana.26940
8. Salvarani C, Hunder GG, Brown RD Jr. Primary central nervous system vasculitis. N Engl J Med. 2024;391(11):1028-1037. doi:10.1056/NEJMra2314942
9. McCall C, Mudali S, Arceci R, et al. Flow cytometric findings in hemophagocytic lymphohistiocytosis. Am J Clin Pathol. 2012;137(5):786-794. doi:10.1309/AJCPP40MEXWYRLPN
10. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. Blood. 2011;118(15):4041-4052. doi:10.1182/blood-2011-03-278127
11. Calabrese LH, Mallek JA. Primary angiitis of the central nervous system: report of 8 new cases, review of the literature, and proposal for diagnostic criteria. Medicine (Baltimore). 1988;67(1):20-39. doi:10.1097/00005792-198801000-00002
12. Birnbaum J, Hellman D. Primary angiitis of the central nervous system. Arch Neurol. 2009;66(6):704-709. doi:10.1001/archneurol.2009.76
13. Beuker C, Strunk D, Rawel R, et al. Primary angiitis of the CNS: a systematic review and meta-analysis. Neurol Neuroimmunol Neuroinflamm. 2021;8(6):e1093. doi:10.1212/NXI.0000000000001093
14. Beuker C, Schimdt A, Strunk D, et al. Primary angiitis of the central nervous system: diagnosis and treatment. Ther Adv Neurol Disord. 2018;11:1756286418785071. doi:10.1177/1756286418785071
15. Raghavan A, Wright JM, Huang Wright C, et al. Concordance of angiography and cerebral biopsy results for suspected primary central nervous system vasculitis: a multi-center retrospective review. Clin Neurol Neurosurg. 2019;185:105482. doi:10.1016/j.clineuro.2019.105482
16. Salvarani C, Brown RD Jr, Calamia K, et al. Primary central nervous system vasculitis: analysis of 101 patients. Ann Neurol. 2007;62(5):442-451 doi:10.1002/ana.21226
17. Miller D, Salvarini C, Hunder G, et al. Biopsy findings in primary angiitis of the central nervous system. Am J Surg Pathol. 2009;33(1):35-43. doi:10.1097/PAS.0b013e318181e097
18. De Boysson H, Zuber M, Naggara O, et al. Primary angiitis of the central nervous system: description of the first fifty-two adults enrolled in the French cohort of patients with primary vasculitis of the central nervous system. Arthritis Rheumatol. 2014;66(5):1315-1326. doi:10.1002/art.38340
19. Nehme A, Arquizan C, Regent A, et al. Comparison of patients with biopsy positive and negative primary angiitis of the central nervous system. Rheumatology. 2024;63(7):1973-1979. doi:10.1093/rheumatology/kead542
20. Salvarani C, Brown RD Jr, Muratore F, et al. Rituximab therapy for primary central nervous system vasculitis: a 6 patient experience and review of the literature. Autoimmun Rev. 2019;18(4):299-405. doi:10.1016/j.autrev.2018.12.002

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Artworks and Articles exhibited at

A TIME OTHERWHERE

at Creative Brain Week
Exhibition Opening

JOHN KELLY

***Head*, 2020. Oil on canvas. 57.5 x 71.5 cm.**
***Camo Landscape*, 2021-2022. Oil on canvas.. 89 x 63 cm.**
***Plato's Cave*, 2024. Oil on canvas. 165 x 101 cm.**
***Evil Kanga*, 2021-2022. Oil on canvas. 74 x 84 cm.**
***Platos Cave*, 2018. Oil on canvas. 46.8 x 38.5 cm.**
***Camo Landscape*, 2018. Pen on paper. 46.8 x 38.5 cm.**
***Evil Kanga*, 2018. Pen on paper. 46.8 x 38.5 cm.**
***Head*, 2018. Pen on paper. 46.8 x 38.5 cm.**
***Kanga DeLarge*, 2024. Oil on canvas. 72 x 86 cm.**
***Stack and Heads*, 2025. Oil on canvas. 92 x 122 cm.**
***Cow up a Tree*, South Reen, 2025. Oil on canvas. 122 x 92 cm.**
Head and Headless, 2024. Oil on canvas. 122 x 92 cm.
***Moonscape*, 2021-2022. Oil on canvas. 61 x 70 cm.**
***Kanga DeLarge*, 2018. Oil on canvas. 46.8 x 38.5 cm.**
***Stack and Heads*, 2018. Oil on canvas. 37 x 45 cm.**
***Cow up a Tree*, South Reen, 2018. Pen on cardboard. 122 x 92 cm.**
***Blue Self Portrait*, 2018. Pen on paper. 38.5 x 47 cm.**
***Head and Headless*, 2018. Pen on paper. 46.5 x 38.5 cm.**
***Moonscape*, 2018. Pen on paper. 41 x 34 cm.**

CHRISTINA TODESCO-KELLY

***Patient's Arm on hospital bed*, 2018. Pen on paper. 54 x 42 cm.**
***Medical equipment stand*, 2018. Pen on paper. 53 x 43 cm.**
***Patient's Broken Glasses*, 2018. Pen on paper. 42.5 x 34.5 cm.**
***Confused Patient*, 2018. Pen on paper. 42.5 x 34.5 cm.**
***Patient's Worn out Slippers*, 2018. Pen on paper. 40 x 33 cm.**
***Patient on trolley from having Brain Biopsy*, 2018. Pen on paper and photograph. 33.5 x 78 cm.**
***Monitor*, 2018. Pen on paper. 40 x 33 cm.**
***Patient Sleeping*, 2018. Pen on paper. 43.5 x 34.5 cm.**
***Patient Identity*, 2018. Pen on paper. 42.5 x 34.5 cm.**
***Drawing on Paper Bag in A&E*, 2018. Pen on paper bag - 53 x 43 cm.**
***Fire extinguishers at Bru Columbanus*, 2018. Pen on paper. 53 x 43 cm.**
***Photograph of pillow with portrait*, 2018. 53 x 43 cm.**

ARTICLES

"I told you I was Ill", *Practical Neurology*, 30 January 2024. (p166 - p168). Kelly, John. 74 x 46.5 cm
"Case Report: Treatment-Resistant Small Vessel Primary Angiitis of the Central Nervous System", *Practical Neurology*, April 2025. (p41 - p46). Wrigley, S., O'Donnell, M., Bermingham, N., Jansen, M., Fanning, N., Tobin, W. O., Brown Jr, R., Merwick, A., Lefter, S. 66 x 59 cm

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CREATIVE BRAIN WEEK
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FIRST NIGHT SELF-PORTRAIT AS SEEN IN THE REFLECTIVE WINDOW IN ROOM 11, ON WARD 3A SOON AFTER COMING OUT OF THE COMA