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Neurological emergencies

Prof Halsey: So, it's my great pleasure to be here, and to try and share some of our expertise on neurological emergencies during treatment for childhood ALL and other hematological malignancies. I'm just gonna bring up my first. So, the intended learning outcome of this session is to know the different ways that chemotherapy-associated neurotoxicity and paediatric malignancies may present and how to formulate a differential diagnosis for this. We're gonna spend a bit of time trying to understand the varied presentations of methotrexate-related neurotoxicity, given that this is one of the most common neuro-toxicities that we see in clinical practice. And I hope at the end of this, you will be aware of the appropriate investigations and supportive care for PRES, stroke-like syndrome, seizures, and some other common chemotherapy-associated neuro-toxicities. I wanted to start by just discussing the spectrum of neurological conditions that you can see in a patient where you're called to the wards, and in an, you know, if you've been called acutely in an emergency with a patient with neurological symptoms, and what kind of might be going through your head in terms of what might be going on. So obviously when the patient has neurological symptoms, there's a possibility that these are either primary neurological, resulting from a problem in the brain itself, or that their brain responds to a systemic problem. Also, when we think of neurological conditions, obviously there are conditions involving the peripheral nerves versus the central nerves, as nervous system. And also, signs may be focal. So, patients presenting with a hemiparesis, et cetera, or they may be very diffuse and global, such as alterations in affect or conscious level. And there's also a huge spectrum of potential causes for neurological conditions. So, I've just listed some of them here, probably not a completely exhaustive list, but we know that infections can cause neurological conditions, metabolic disturbances, vascular problems, such as bleeding or clotting, drugs, radiotherapy, problems with the immune system, the actual tumour itself, and pre-existing neurological conditions that the patient may have had prior to their cancer diagnosis, such as epilepsy, autism, and other conditions. And of course, the other thing is that there may well be quite a bit of interplay between this. So, one of the concepts, I think, that's important to think about is that not all patients who expose to a chemotherapy agent have a neurotoxic side effect. And what determines whether you have that side effect may be partly to do with your genetic susceptibility or particular things with the dose you received, but also may be very much to do with having other things that might predispose you to getting that side effect. So, for example, having co-existent infection and a high temperature might lower your seizure threshold when you're exposed to a medicine that might cause seizures. So, if you didn't have your temperature and your infection that day, you might not have had a fit, but that day, because you had a high temperature, or had a low sodium or something like that, you did fit. So, it's not necessarily as a single cause. There may be a multifactorial etiology. I also just wanted to start by saying what we're not covering in this lecture, given that we've only got half an hour or so. And a disclaimer, if you like, that I am not a neurologist. So those of you who are hoping to get a kind of neurology input on this, you know, I'm very much seeing this from the perspective of a practicing paediatric haematologist and see it looking at the chemotherapy-associated neuro-toxicities. So, we're not going to cover neurotoxicity that's secondary to the bulk of the underlying cancer, the

neurosurgical management of brain tumours, for example. That's probably a subject for a separate lecture. We're not gonna cover the side effects of cranial or craniospinal irradiation. We're not gonna cover neurotoxicity that's secondary to infections, very well covered in many textbooks, and meningitis and encephalitis, et cetera. We're not gonna cover particularly metabolic insults that are systemic rather than CNS related, although we may touch on some of these, particularly in the discussion. We're not covering primary CNS bleeds, either due to the tumour or thrombocytopenia or trauma, et cetera. And I'm afraid, I don't think we've really got time in this lecture to cover in any kind of detail neurotoxicity related to immunotherapy. Again, you know, a very, an area that kind of requires a teaching session of its own. And there are some very good reviews in that area recently. So worth reading if you're particularly interested in that. But obviously all of these things are important. And if you're called to the ward to see a patient with neurotoxicity, these are parts of the differential diagnosis. So, we're giving you a flavour of chemotherapy-associated neurotoxicity here, not necessarily all these other things that may be going on in paediatric haemato-oncology patients when they present acutely. So, I wanted to just start with a kind of impression of how common chemotherapy-associated neurotoxicity is, and the kind of spectrum that we see to do specifically with chemotherapy here. And so acutely, we can see a number of conditions, most of which we will cover today. Seizures, stroke-like syndrome, PRES, neurocognitive disturbances, thrombosis, mood disorders, coma, encephalopathy, et cetera. But also, there's quite a chronic burden of neurotoxicity in terms of late effects, effects on neurocognition, behaviour, quality of life, and potentially a link between chemotherapy exposure in childhood and accelerated aging within the CNS and the possibility of early-onset dementia. And if you look, this is the UKALL 2003 ALL trial, looking at the serious adverse events. And you can see that between 8 and 12% of children had encephalopathy reported as a neurotoxic SAE. So, encephalopathy encompassed this whole range of acute conditions, not just a primary confusional state. And I think one of the things that will emerge throughout this talk is the theme that chemotherapy agents tend to produce different patterns of neurotoxicity. So, I've listed here some of the common neurotoxic presentations and the chemotherapy agents that they're associated with. So, sinus thrombosis often asparaginase related, stroke-like syndrome, methotrexate, PRES often associated with vincristine and steroids, isolated cerebellar symptoms, as seen in agents such as Nelarabine and Cytarabine. Seizures can be pretty much any of these. Psychosis is often very strongly related to steroid therapy. There's a very specific ifosfamide encephalopathy. And of course, new agents are being used all the time. And these may well have an unexpected and unknown neurotoxic profile. But I think it's fair to say that this is a ward quite simplistic, because a patient you're asked to see on the ward is often on multi-agent chemotherapy, and they've often been exposed to a number of these. So, a child going through ALL induction will have had asparaginase, methotrexate, vincristine, and steroids all at the same time. So, although identifying the causative agent is useful, sometimes it's difficult when you are acutely see a patient to work out which one of these agents is causing the neurotoxicity. And the other thing that will emerge during this talk, I think, is that there are differences in instance in these different chemotherapies, across different trial groups who are treating the same disease. And that may reflect different use of these chemotherapy agents, different doses, different scheduling, but it also may reflect a little bit difference in classification, particularly in the stroke-like syndrome PRES space, which we will go on to explore. It's important to kind of think about acute neurotoxicity, not just for the patient in front of you, but also because it may well have an impact on the outcome of the patient. So, this is reasonably old NOPHO data here, but very convincing data that shows that patients who had suffered PRES during their chemotherapy regimen actually had an inferior overall survival from their leukaemia compared to these patients in the dark line at the top that didn't suffer from any neurotoxicity. And one of the reasons for that is potentially shown in this study here, which looked at patients treated on different ALL protocols and showed that the patients who had neurotoxicity ended up getting significantly less intrathecal methotrexate doses than those who did have neurotoxicity. So some of the impact on treatment outcomes may actually be because we modify our anti-leukemic treatment in response to the neurotoxicity. So, we need to be very careful about what we're doing there. May not just be the methotrexate. It may also be the use of supportive care, such as giving enzyme-inducing agents as

anti-epileptics, like phenytoin, which may then reduce the efficacy of other chemotherapy. However, in more modern protocols, both more modern noted protocols and in our UK experience, if you are good about re-exposing patients that you can where it's safe to re-expose and missing and catching up on missed doses of chemotherapy, and you avoid these enzyme-inducing agents as anti-epileptics, in fact, you can have outcomes that are the same. So, this is the UKALL data of patients with and without those 8% of patients who had neurotoxic side effects, actually had the same outcome as other patients. So, the impact on outcome is variable and depends on what you do with the patient. It's not inevitable. So, I just wanted to start with just one slide on the ifosfamide encephalopathy before I move on to talking about methotrexate. So ifosfamide encephalopathy, not something we commonly see in haematological malignancies, but certainly used for [Audio Not Clear] tumours. It's seen in about 10 to 30% of patients, either during the infusion of ifosfamide or shortly after. And often it presents with a kind of an acute confusional state or reduced level of consciousness, but can also cause the opposite, a kind of agitated, hallucinogenic state with a kind of psychosis, and also potentially muscle twitching. And it is potentially very serious, can occasionally result in coma and death. If you do an EEG on these patients, it shows generalized slowing and triphasic waves. And the likely cause is the metabolite of ifosfamide chloroacetaldehyde, which leads to neurotoxicity and cerebral glutathione depletion, as well as inhibiting mitochondrial electron transport. There is a reported association with patients who've had previous cisplatin, or have impaired hepatic or renal function, or have taken other medications for supportive care, such as aprepitant. And those who carry a polymorphism in one of the drug-metabolizing enzymes. And so, if you have a patient with ifosfamide who acutely develops encephalopathy, the management of that patient is to stop the infusion, to correct the fluid, any fluid and electrolyte imbalance, obviously optimal supportive care. And you can consider intravenous methylene blue, although actually the evidence base behind that is relatively weak, but it does seem to be something that's recommended and certainly is unlikely to do any harm and may do some good. And in fact, methylene blue can be used in subsequent courses to try and prevent recurrence. So, I just, before I move on to the main part of the talk, I just wanted to remind people that they can ask questions at any time, and we will kind of deal with those questions at the end but do pop them in the chat so that we can accumulate chat questions as we go along. So, I want to spend a little bit of time talking about methotrexate. This is predominantly the most neurotoxic drug we use in childhood leukaemia therapy, also used obviously in other tumours sometimes. And it has quite a spectrum of neurological presentations. So, acutely, during the administration of methotrexate, particularly intrathecal methotrexate, you can get a syndrome which occurs very soon after methotrexate, or during methotrexate administration, with nausea, vomiting, somnolence, and headaches. Sometimes confused or difficult to differentiate from a post-LP syndrome. However, actually the most dramatic neurotoxic effects of methotrexate are seen in the subacute setting. So, acutely, this was mainly seen with very high doses of methotrexate given intrathecally, which we don't really give so much anymore. So, this is less prominent at the moment. But we do certainly see this subacute presentation, usually between two- and 21-days following administration of methotrexate, either IV or intrathecally, or even very occasionally orally. And you can get this syndrome of stroke-like episodes, which I'll come on to discuss. Or in fact, you can also get asymptomatic leukoencephalopathy seen on MRI scanning. So, it's not necessarily symptomatic, this subacute methotrexate neurotoxicity. And we also know that methotrexate is associated with adverse chronic neurological outcomes, neurocognitive outcomes. The association between these acute events and the chronic event is not clearly understood. So, I could spend a lot of time discussing mechanisms of methotrexate neurotoxicity, which you'll be glad to say, I'm not going to. But we know that some methotrexate toxicity is just related to dose. So, if you give very high dose of methotrexate, you will get more neurotoxicity. If you inadequately rescue patients, you can also get more toxicity in general and also neurotoxicity. We think the acute nausea, somnolence and vomiting is probably due to an acute release of adenosine due to the metabolism of methotrexate. But the more subacute may actually be related to high levels of homocysteine, and essentially methotrexate inhibits dihydrofolate reductase, which reduces the supply of methyl-tetrahydrofolate, which is the building block for purine and pyrimidine synthesis. This is

how it kills leukaemia cells. But if you block this reaction, what you end up is an accumulation of homocysteine and the reduction in methionine. And both of these may be responsible for the neurotoxicity. Too much homocysteine is broken down into excitotoxic glutamate analogues that act on the NMDA receptor. And this is important because this can potentially be blocked by memantine or dextromethorphan which we'll come on to discuss. Myelin sheath production and methionine is also thought to be important. And in fact, there was a very interesting paper in Cell recently that you can read at your leisure, showing that defective myelination underlies methotrexate toxicity in adult patients undergoing treatment for colic tumours. However, there's also potentially drug interactions that may affect this process, and we'll come on to discuss them. And genome-wide association pathways suggest that additional mutations or polymorphisms in genes in your developmental pathways may predispose children to toxicity for methotrexate. So, I wanted to start with methotrexate stroke-like syndrome. I've already mentioned that this occurs usually within 21 days of methotrexate, and it's pretty much exactly what it says in its title. It's a stroke-like syndrome. So, these children present with what looks like a stroke. It may be a hemiparesis. It may be a facial palsy, another cranial nerve palsy, and may often be disturbances in either a dysphasia or emotional ability or other kind of disturbances of affect. But what's a little bit different from a stroke in older patients that we might see without cancer is that actually these symptoms are very labile and transient. So, the symptoms tend to wax and wane. And, if you've seen a patient with a classic stroke-like syndrome, you won't ever forget it. 'Cause you go down to A&E, they've got a facial nerve palsy, you admit them to the ward, you walk up the stairs, get to the ward, the facial nerve palsy has got back to dense left hemiparesis, for example. Few hours later that then resolves and maybe they have some emotional ability. So, you get this very kind of transient and waxing and waning and varied presentation over the course of hours to days. If you do a CT scan, it's usually normal, but MRI scans show this characteristic leukoencephalopathy, often periventricular like this, although it's best seen on diffusion-weighted and T2-weighted images. You usually get complete resolution within seven days. And we're not really sure what the risk factors for it are exactly. It seems to be commoner in older children, particularly teenagers, and commoner if you can currently administer Ara-C or cyclophosphamide, although that's not proven, that's data from the UK group. But it's also got some rather strange things about it. Like it doesn't necessarily occur on your first methotrexate exposure. So, if it was a genetic predisposition, you'd expect your first dose to cause it, but actually it could be your third or fourth dose. It doesn't clearly relate to your methotrexate level. And usually if you've had it before, actually if you re-expose the patient to methotrexate, they don't get it again. So, we're really not sure entirely why some children get this and others don't. In terms of managing stroke-like syndrome, wherever possible, you should try and establish the diagnosis using MRI scanning with diffusion-weighted imaging. Obviously exclude alternative causes for your symptoms, such as an infection or CVST, haemorrhage, PRES, exposure to toxins, et cetera. As I mentioned, many patients will have spontaneous resolution of symptoms, but there are two drugs that have been used to treat this condition. It's extremely difficult to test whether they're efficacious or not because the symptoms resolve spontaneously. So here is some evidence with dextromethorphan, which acts on that NMDA receptor. This is the biggest case series to date. And you can see that these patients have a variety of different neurological symptoms, and they were given dexamethasone, dextromethorphan, sorry, but what you can see here is, although it was said to be efficacious in that they got better, the time to getting better is really, really variable. And it may be that these patients that got better in 10 days, 24 hours, et cetera, may well have got better anyway. So, it's difficult to know whether the dextromethorphan made a difference. Aminophylline has also been used. There's an older paper in the Lancet. But again, if you look here at what the symptoms of these patients were, these are much more suggestive of acute methotrexate toxicity, not stroke-like syndrome. And aminophylline effects adenosine release, which is higher in these patients who'd received methotrexate. And now we have brought our methotrexate doses down, we see the syndrome much less frequently. But if you do have a patient who has severe acute symptoms, then aminophylline may be more appropriate. We talk about neurological emergencies. So asymptomatic leukoencephalopathy is obviously less of an issue, but it's just worth noting

that in the large St Jude's series, although only 3.8% of their children had overt neurotoxicity, when they did serial MRI scanning on all of their patients, 21% of them had leukoencephalopathy on their MRI scan, even though they didn't have neurological symptoms. And of these, about three quarters of them actually had persistently abnormal MRIs at the end of therapy. The obvious question is are these the patients that go on to develop long-term neurocognitive deficits? And the later follow-up study from St Jude's suggests that that may be the case, although the relationship is not completely clear-cut. Chronic neurotoxicity is very common. Up to 40 to 60% of survivors of ALL have subtle neurocognitive defects, even if not treated with cranial radiotherapy. And it appears this is related to SNPs involved in folate pathways and oxidative stress. And I mentioned earlier about the possibility of accelerated aging within the CNS. Methotrexate can also cause seizures, but seizures are quite common, not just with methotrexate, but throughout ALL therapy. They're seen in up to 10% of patients, often occur early during treatment. Most occur within the first 18 months; this is an ALL cohort here. And they have a diverse etiology related to chemotherapy and other causes, including electrolyte imbalance, such as hyponatremia. But there is data emerging now that the patients with idiopathic seizures, so where you couldn't find an infection or a thrombosis or a low sodium, et cetera, are more likely to have leukoencephalopathy with subsequent neurocognitive deficits. And that makes us think that actually, maybe that methotrexate neurotoxicity is a little bit like an iceberg. We have lots of patients who have this leukoencephalopathy without any clinical symptoms. We have patients who might present just with seizures. And then we have these patients at the top that actually have the full-blown stroke-like syndrome. So, we're seeing quite a spectrum of different responses to the same chemotherapy agent. In terms of the management of seizures, this is not just methotrexate, any seizure in a patient with ALL. Obviously, you want to try and prevent prolonged seizures, prolonged seizure activity, and identify and where possible treat the underlying cause. But many seizures are brief and self-terminating so don't necessarily need therapy, but obviously if they're prolonged, then local protocols for benzodiazepines and other anti-seizure medications should be followed. I mentioned at the beginning about really being very assiduous about avoiding anti-epileptics that induce Cytochrome P450, and certainly we and others have found that Keppra is a very good choice if you do need maintenance anticonvulsants. It is possible to re-expose the patient to the chemotherapy agent once the seizure activity is under control. And trying to prevent seizures in the first place can be done by careful attention to fluid balance, glucose and electrolyte levels, and hydration fluids should be isotonic where possible and have regular monitoring of sodium levels. So, I then just wanted to move on to posterior reversible leukoencephalopathy syndrome, otherwise known as PRES. So, PRES is a clinical radiological entity characterized by seizures, headache, altered mental status and visual impairment. The MRI tends to show these subcortical or cortical oedematous regions in the parietal occipital region cells, hence its name, posterior. It's usually associated with hypertension. And what we think is happening pathologically is that there's an interplay between endothelial dysfunction, which is associated with the use of chemotherapy and steroids, hypertension, and the leukaemia, or overall causing leaky events, leaky vessels, which lead to vasogenic oedema. There are quite a lot of risk factors, we think, for PRES, and actually, there's a very wide variation between trial groups, which may reflect differences in the way that the chemotherapy is delivered and chemotherapy doses. So, we know that high doses of vincristine is probably associated with this and leads to symptoms of constipation and hypernatremia in addition. Steroids are associated with it, and also aggressive hydration and the use of azole antifungals, which do then also increase a vincristine toxicity, are probably associated. And one of the groups with the biggest experience of PRES is the NOPHO group. And here is an up-to-date paper on PRES from the group, showing some clinical features of PRES and also some risk factors. So, it appears to be commoner in T-cell than B-cell, commoner in older children than younger children. You can see that the commonest symptom is seizures, but you also see encephalopathy, and these symptoms, constipation, abdominal pain are very common, but also is coexisting infection. And hypertension is seen in most, but not all children. And if you look at when PRES occurs, it tends to occur early in therapy in this kind of early window. So not later on. But those of you who've been kind of listening carefully, will have kind of worked out that actually there's a lot of overlap between the symptoms of PRES

and stroke-like syndrome. So, I've shown in green the symptoms that are the same, when you look at the consensus definition for PRES and stroke-like syndrome published in the Lancet Oncology recently. And the differences are shown in red here. But sometimes when you go to the literature and look at the descriptions of PRES, for example, they will include patients with hemiparesis, et cetera. And one of the reasons for that is it's actually quite difficult to distinguish them radiologically so they can look very, very similar. But there are new imaging techniques that allow us to have a much better differentiation between these two. So, it's thought that PRES is due to leaky vessels, due to this endothelial dysfunction. And so, there's increased water diffusion, whereas stroke-like syndrome due to the release of homocysteine actually causes a contraction of the vessels and reduced water diffusion. So, if you do these tests known as diffusion-weighted imaging, or you use the T2 flair imaging technique on MRI, you can actually distinguish these two. But one of the problems is when you're trying to remember that, but actually the diffusion-weighted imaging is turned into an apparent diffusion coefficient. And when you have increased diffusion, the apparent diffusion coefficient is reduced. So, when it's restricted, it's darker on the software. So, you end up with a lot of confusion and it leads to confusion in reports. So just to be aware of that when you're doing imaging, that it's easy to mistake these two conditions. In terms of treatment for PRES, we aim to treat the hypertension, aiming for certainly about 10 to 20% drop acutely, and then a slightly slower drop into the normal range, withhold any causative agents, obviously withhold the vincristine until recovery, if possible, maximize supportive care, including platelet transfusions to minimize the risk of secondary haemorrhage, postpone your intrathecal treatment until you've normalized findings and the MRI is looking better. But where possible do try and catch up on missing doses. So, moving to a close now, I just wanted a couple of slides on other conditions that we sometimes see. Cerebral venous sinus thrombosis, strongly associated with asparaginase therapy in combination with steroids, but also patients often have other procoagulant risk factors. So, immobility, infection, dehydration, potentially age as well. It's seen clinically in about 1 to 2% of patients going through ALL therapy, but actually protocols that do routine scanning do see asymptomatic cerebral venous sinus thrombosis. So, the real instance may be higher. Usually occurs during consolidation phase of ALL, and presents symptoms such as headache, nausea and vomiting, fatigue, seizures, depressed consciousness, or cranial nerve palsy. So very similar to what we saw with the stroke-like syndrome. Can be diagnosed on a CT scan, better seen on an MRI scan. And you can see, as in this image here, that there's sometimes concurrent haemorrhage and infarction in the territories in which these blocked vessels are serving. It can be associated with low antithrombin levels, secondary to the asparaginase treatment, but not always. And actually, the coagulation profile in patients with CVST can be very, very diverse, and you can sometimes even see it with normal D-Dimer levels. We treat it with low molecular weight heparin at therapeutic dose for at least three to six months, and certainly until three weeks after the last asparaginase dose, and then provide the patients with prophylaxis during high-risk periods. If there's extensive haemorrhage at original diagnosis, it's reasonable to withhold anticoagulation and re-scan, but some studies have shown that outcome is poor if patients who didn't receive anticoagulation. And therefore, limited haemorrhage, as is seen here, is not actually an absolute contraindication to anticoagulation as long as the patient supported with platelets. And it's suggested to withhold the asparaginase for at least four weeks, re-scan to assure that the clot is stable, and proving before planning to re-expose. Although again, re-exposure is allowed, and I just direct your attention to a very good management guideline on venous thrombosis in general in ALL, but they have sections on CVST with all the evidence presented there. And then I wanted to end with steroid psychosis. We do, we see this in some of our ALL patients, pretty much all of our ALL patients have some form of steroid-related neurotoxicity, from very mild symptoms, as well, exemplified by this poem here written by the older brother of a child with leukaemia going through ALL therapy on their dexamethasone, and you will recognize that, if any of you look after patients with dexamethasone. This kind of this real ability of mood that even young patients have, but can also be very severe with acute psychosis. This acute, looking really at the very severe end, the steroid psychosis, it seems to be commoner with dexamethasone, commoner in the TYA population, does usually could during periods of active high-dose steroid treatment like induction,

but it can actually occur after you've stopped the steroids, up to a week or so later. You manage it by trying to cease the steroids if you can, or at least dose reduce. Benzodiazepines can be helpful, obviously supportive care and involvement of your psychiatrists and psychiatric nurses. And some anti-psychotics, particularly risperidone have been reported to be useful. And again, this is an excellent review that summarizes all of this. So, I wanted to end with just a kind of practical approach. I've given you a lot of different potential causes here. But when we are looking at an ALL patient, and you're asked to call to see them with acute CNS symptoms, then obviously you want to stabilize vital functions, treat seizures, do a blood count, infections, electrolytes, coagulation, imaging, et cetera. And then kind of what the most likely diagnosis is depends a little bit on what your chemotherapy is. So high-dose methotrexate, or intrathecal methotrexate. Here's the symptoms of stroke-like syndrome. Asparaginase, have you thought of sinus venous thrombosis? Vincristine, what about PRES? And then none of those, there's also all these other things to think about. And then the investigations that you should do for that. And then the potential treatments are shown here. So, the take home messages from this talk. Neurotoxicity during treatment is common, and it may be a direct or indirect side effect of chemotherapy agents or the underlying cancer. So, when we think about indirect, we're thinking about things like infection, hyponatremia, et cetera. There's a complex interplay between genetic drug and environmental factors. Careful attention should be made to avoiding drug interactions and fluid and electrolyte disturbances, which may cause, reduce the threshold for getting neurotoxicity. If you do a thorough history or review of the medication charts and the phase of treatment and neuroimaging, that'll usually help you with establishing the most likely cause. And management is largely supportive, and the evidence-based treatments are lacking. So, I'll just stop here. And I'm very happy for me to just thank some of the people who contributed to some of the work behind this, but I'm very happy to take any questions.

Prof Harila-Saari: Thank you very much, Chris. This was a wonderful overview of this important topic, and quite a common problem we see in children, especially with leukaemia and ALL. Please send your questions to this question and answers, or you can also use the chat. I thought we'd start with a couple of questions. What do you think of the role of seeing as leukaemia as a predisposing or as a cause of neurotoxicity?

Prof Halsey: Yeah, that's a very interesting question. So, I think both for, certainly for PRES, and actually for many of the other syndromes that I described today, they tend to be front-loaded, seen at the beginning of treatment. And obviously at that time, a lot of things are going on. This is a time when the patients are acutely unwell. So obviously all these other things, like having infection, electrolyte disturbance, fluid balance problems, et cetera, may well be going on there as well. But it may also be that the presence of leukaemia in the leptomeningeal space is causing an inflammatory phenotype that lowers patient's threshold for neurotoxic symptoms. And actually, the main topic of my research is looking at CNS leukaemia. And it's quite clear that most children do have CNS leukaemia at original diagnosis, even if we don't see it on cytospin. So, you might say it's easy to answer that question ‘cause is neurotoxicity commoner in CNS 3 patients, patients who have CNS leukaemia, but actually there are an awful lot of patients with CNS leukaemia that we don't see on cytospin. So, it's not as easy as teasing that out. I think for PRES in particular, CNS leukaemia probably does play a role in terms of the leaky vessels, the endothelial dysfunction, et cetera, because when we measure inflammatory markers in the CSF and protein in the CSF acutely, these things are high in patients with leukaemia at diagnosis. Obviously, as we go through, we've treated the CNS leukaemia. So that burden goes down and therefore that influence wanes.

Prof Harila-Saari: Thank you. Then we have a question from an attendee. "Thank you, Chris. Long-term deterioration of neurocognitive functions after methotrexate is very worrying. What is your opinion on prophylaxis with dextromethorphan?"

Prof Halsey: Yeah, so that's an excellent question. It certainly is worrying. One of the issues is, leukaemia has only really become curable since the 1960s, and the peak age for leukaemia is age two to five. So even our very first patients who are cured, you know, are only just approaching their kind of sixties now. So, we

don't really know what's gonna happen with these patients as they get older. And for the first 20 years or so of leukaemia treatment, pretty much everyone received radiotherapy, which we know has significant long-term impacts on neurodevelopment. And therefore, in order to find out what's happening with chemotherapy-only regimens, we really need to look at patients who were treated in the 1990s, 2000s. And they're not gonna be old enough for another 10, 15 years. So, I can't say I have evidence from patients that chemotherapy-only regimens definitely cause accelerated aging within the CNS. But if you do scans on patients in their twenties and thirties who received leukaemia treatment as a child, you do see loss of white matter volume and changes that do look like the very early changes you might see in kind of accelerated aging, pre-dementia stages, et cetera. What we don't know is whether they're gonna be static, or whether it's gonna be a progressive decline. So yes, it is very worrying. In terms of whether dextromethorphan is the right thing to prevent that, I'm afraid, I think probably not. I think the longer-term leukoencephalopathy, loss of white matter volume and things are related to these, more to do with these disturbances of myelination and glial activation and things, which are inevitable side effects of methotrexate. The key to sorting this out is to move away from using methotrexate. It's a horribly neurotoxic drug, and we really need to try and find new agents for CNS leukaemia that don't damage children's developing brains, and that's the way we're gonna really fix it. However, there's a huge amount of research being done now in the dementia space, lots of new agents, lots of ideas about early intervention before patients actually show symptoms of dementia. And it may well be that actually our leukaemia cohort, we should be really advocating for them to be scanned and to look at that and to be included in these kinds of trials. And that may be our best option at the moment for this cohort coming through.

Prof Harila-Saari: Thank you. Then there is an interesting question. "What about neurotoxicity in children with AML?"

Prof Halsey: Yes. So, we don't see it nearly as commonly. You can get neurotoxicity from cytarabine, which is one of the main components of AML therapy, but the main, obviously there's always infectious toxicity, but the main toxicities we see with AML treatment are more related to cardiac toxicity. So that probably reflects the drugs that we use. But of course, that points back to your original question, Arja, about the role of CNS leukaemia, and we know that CNS infiltration's less common in AML. So maybe that's another factor that says we see less neurotoxicity in AML. But yeah, that's my thoughts on that.

Prof Harila-Saari: Thank you. You mentioned that genetic risk factors for methotrexate narrow toxicity. Are there any genetic risk factors for the other neuro-toxicities?

Prof Halsey: So, we haven't discovered any that I'm aware of, unless you know of any, Arja, for PRES. Do you have any genetic risk factors for PRES?

Prof Harila-Saari: No. I have not seen any, no.

Prof Halsey: Obviously, for peripheral neurotoxicity, and vincristine, there's a very nice, a very elegant study showing that there's a polymorphism in a gene that very strongly predicts for methotrexate peripheral, sorry, for vincristine peripheral neuropathy, but I'm not aware that that polymorphism is associated with PRES. So, no, I don't think, there's a lot of stuff to discover there. So, one of the things that Arja and myself are involved in is a really big international effort across the whole of the world, really, 24 countries, I think are involved, trying to collate all our cases of neurotoxicity, because these individual neuro-toxicities are rare. And within one individual country, or one individual study group, we just don't have the numbers to look at these genotype, phenotype associations, just 'cause the case numbers are so small. But by combining together we can potentially do this. And through a great effort, and from lots and lots of people, we've managed to collect together nearly 1,400 cases of neurotoxicity spanning stroke-like syndrome, PRES, all the things that I've been discussing today, including steroid psychosis, in fact. And we've been trying to understand more about the natural history of these conditions, but also potentially the next phase will be to move on to genotyping these patients and comparing them to controls within the

trial groups that did not have neurotoxicity. So that's gonna be a really exciting phase of the project, to see if we can predict which children will and won't get neurotoxicity.

Prof Harila-Saari: Thank you. Then we have probably four minutes left. So, I have one question about the steroid psychosis. Sometimes it feels that it's very much related to sleep, that they cannot sleep. And after being awake for too long time, and especially the small children, getting almost psychotic, or psychotic after being awake and not able to sleep maybe a week or two. What is your experience of these anti-psychotics or benzodiazepines in treatment, or should we try to avoid development of steroid psychosis by early intervention with melatonin or something else? How do you think about? Because it's really awful for the families. It's really gutting when the child is not sleeping and is having the tantrums and not behaving at all as usual.

Prof Halsey: Yeah. It's so interesting. Yeah, you're absolutely right. The cases that I've seen have often been associated with, they've often occurred in the middle of the night. Seemed to always occur at three o'clock in the morning, something that you're called. And, you know, we are associating patients who have kind of had a build-up, they didn't tend to have been completely fine and then suddenly they're psychotic, as you say, there are often these kinds of pre-existing, kind of, agitation and hypervigilance and these kinds of things. I think it's an excellent suggestion. I think we need to know a lot more about, not so much documenting the adverse neurobehavioral effects of dexamethasone, but actually doing something about it. You know, it's all very well to say, oh, it's awful. And I think, you know, if you talk to families going through ALL treatment, it is the steroid, you know, we give pulses during maintenance. This is the thing that impacts quality of life, not just for the patient, but for the entire family. And I found that poem very powerful when I read it in the review. You know, about what it's really like to live with a child who's on dexamethasone. And, you know, it is something that I think we do need to look at intervention studies for, and because it's so common, actually it would be reasonably easy to, you know, be able to recruit enough patients for these, for these kinds of studies, not so much, obviously psychosis isn't common, but the other neurobehavioral, the agitation, the lack of sleep, these kind of things are common. So, I think that would be a very interesting area to look at.

Prof Harila-Saari: Thank you so much. And thank you for all the participants and the questions we got. And I think it's getting seven o'clock. So, we are on time.

Prof Halsey: Thank you.

Prof Harila-Saari: Thank you. Bye-bye.