Selected Topics in Psychology Neuropsychology
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Module - 5
Lecture - 26
Brain Microstructural Correlates of cognition in Vitamin B12 Deficiency

Actually in this one hour I will try to cover the vitamin b deficiencies and the refract on the brain structure mega structure and brain function. Now what we find in this country as well as the rest of the world this is that vitamin b twelve and b one there are very commonly deficient in individuals and the belief all the b twelve deficiency you see more in the vegetarians and non-vegetarians elderly. So, do not take much meal they do not have enough meals to take those things and that's what they are deficient and they develop a dimensions early dementia or something to that extent even alzheimer's disease people say the b twelve is associated with the alzheimer's and one of the things people try to do is to add b twelve to their treatment beside the cyano treatment of alzheimer's disease similarly it has been shown in the neonates and children who are been dependent on the milk from the brest not taking the dairy rich b twelve milk.

So, they are the one who has to get deficiency in b twelve the mother is deficient the child gets deficient and elderly it grows the age the age groups the adult is the group one which is not very much studied most of the work has been done on the developing brain as well as a extremes of age, but do not in the one which are adult they and mostly these patents come to you with some neurological deficient they come with the sensory problems.

Some weakness of the limbs and the very, very, very known specific things you know which if you go the largest caesarean it picks up the things and you ask for a b twelve you ask foraimagine and imaginemay not always be a very productive you know in answering these questions and that is the region I thought this is one area which is easily correctable have an impact on the cognitionand no cognition has been started in the adult population withb twelve it has been started in elderly east there in lot of studies from the west which I have the coached. So, elderly they do all kinds of things and the same with the b one the thiamine deficiency is very common is very common typically we say even

in the west what defect it has is lot of alcoholics in thiamine deficiency people who take alcohol they have a liver dieses they have liver damage.

And they have thiamine and wernicke's encephalopathy which you all know as a psychologist wernicke wernicke's korsakoff syndrome and that is very commonly associated with all marchiafava bignami disease where again there is a thiamine is associated with that. So, I thought I will combine thiamine we have done some work with thiamine doctor rothod and me have worked and we quantify the blood thiamine is a very difficult to quantify no lab does that actually. So, we struggled we had a grant from icmr we struggled a lot initially in a how to quantify we tried different methods different means and we bought a column we have to send it back it not working properly in hplc. And finally, we found method with more easily doable and we quantify and we published work actually. So, with these I start with the b twelve to begin with and then I move to the b six little bit and just to give you an idea how those. So, innocuous vitamins can cause having to adrenal systems and without you realising there is a casual normal.

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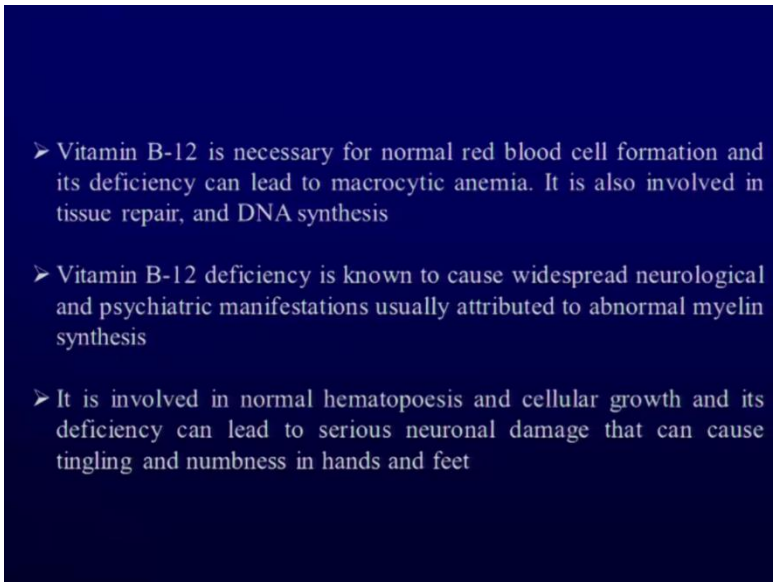

So, we all know vitamin b twelve is necessary for normal red blood cell formation and its deficiency can lead to the macrocytic anaemia that is a classic thing which occurs in the size of the r b c increases they called a macrocytic anaemia, and one of the subcomponent of microcytic in the megaloblastic anaemia it is also involved in the tissue repair and the dna synthesis it is a cofactor coenzyme to many of things you know as a in

the chemical point of view it is known to call wide spread neurological symptoms and wide spread psychiatric manifestation usually attribute to the abnormal myelin synthesis. So, it is the wires the connecting wires which can defective and this is one of the reason we study the wires in our study and to see that how the wires get effected even when of standard imaging this they look absolutely normal.

Now, it is involved as we as we mentioned in the haematopoiesis that is a blood formation cellular growth and its deficiency can lead to serious neuronal damage and they cause and can cause tingling and numbness in hands and feet that is the typical presentation people call it as a as a peripheral neuropathy or a psychological problem then no problem the imaging normal you know these are the world who get toaster out and they really have serious problems there are very few reports which mention the reversibility of leuko encephalopathyon the brain only once in a while you will find the report case note verifying there were changes in the brain which were like white butter changes and they reversed with b twelve injection, but everybody who gets those kind of changes not a b twelve and everybody with b twelve hardly have a changes of brain ninety nine present of patients sufferers the b twelve deficiency hardly have changes which is visible on the brain. So, it is difficult to and the only way to prove is by doing the level blood level.

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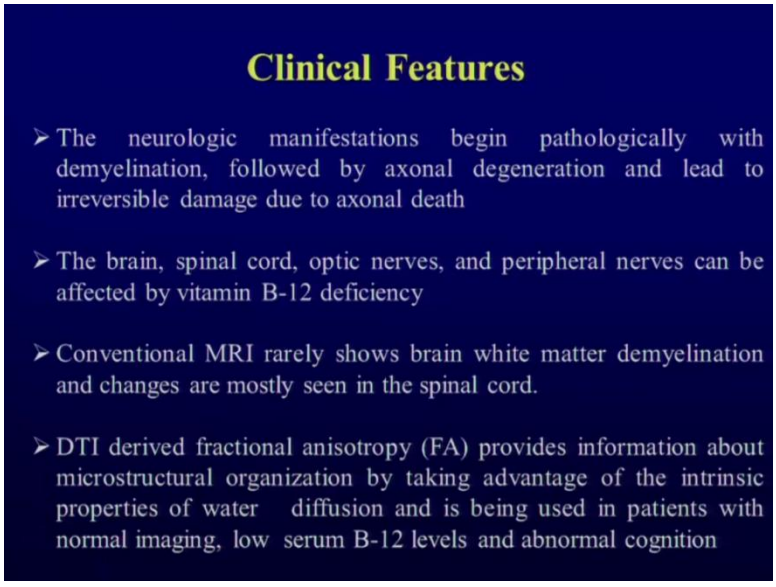

So, this is all the pathology stats it begin with the demyelination axonal degeneration and irreversible damage if the damage becomes too extensive the reversibility not there it be not reverse especially the spinal cord the limb may not come back to normal they may still have some deficiency, because once neuro degeneration occurs after the axonal degeneration occurs that is going to be very difficult to repair brain spinal cord optic nerve and the peripheral nerves can be affected conventional MRI rarely shows brain white matter demyelination, and the changes are mostly in the spinal card if at all. So, that is why we thought, let us look at the tractography and look at the micro-structural changes in the fibre bundles how how they behave and how they are different from the normal brain parenchyma in a b twelve deficiency even when they are absolutely looking normal in vision

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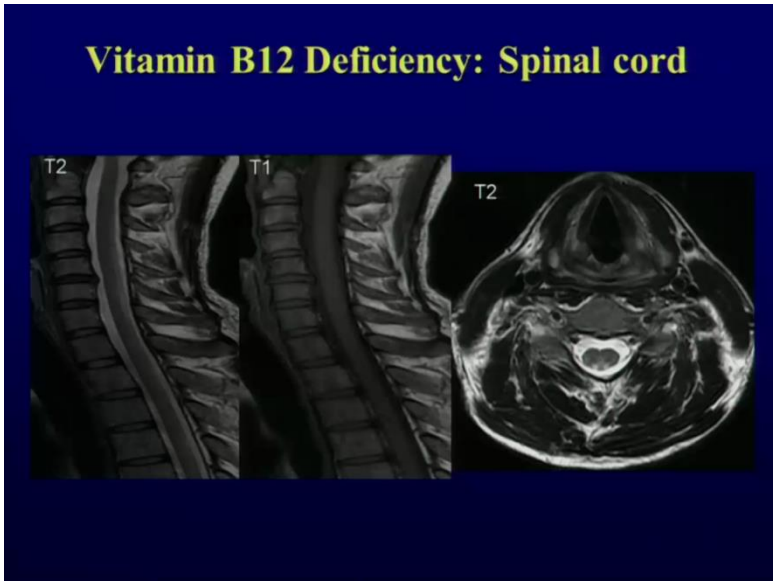

Now, this is a classic example of how do you look at the b twelve deficiency can you. So, this is what happens is that if you look at this if you look at a posterior part of the cord if you can see here this is definitely brighter than the interior part of the cord and if you look at the axial view you find the posterior columns the poster little columns are in normal, and this is what if you know as a psychology this is what we call as a sub secure comandaration to the cord in the by doing the this is the classical picture of b twelve deficiency, but this classical picture is seen in a ottentual present of patents with a clinical symptoms majority of the patients have a normal some have very extensive some have Cord atrophy, but this picture is there definitely I can say a radiologist this is a sub

recommendation to cord, but this picture is rarely you know visible in the b twelve deficiency

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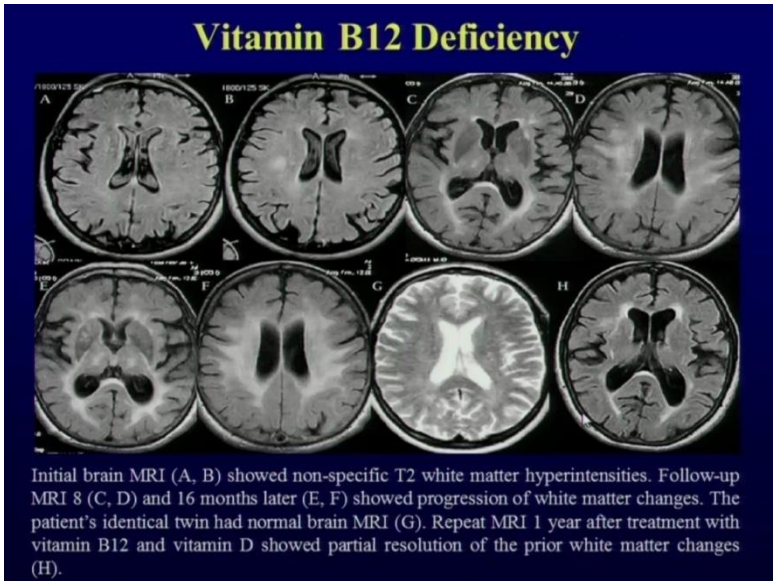

Now, this is what is the white matter changes our toughing about you got a graph white matter changes you can see this absolutely bright signal all around and when you treat them they tend to be gross this is a classic picture of the b twelve and this is seen once in a life time. So, you do not see definitely you know and now if I is see that I cannot see this is a b twelve I cannot say this is b twelve because this is for nonspecific vibrated damage it can occur anything in anything.

So, I call it like a toxic demodulation and we call it as a metabolic demodulation I will not call it b twelve deficiency, because this is not a typical feature of b twelve deficiency. Now, what have done is we have done some of the standard this psychological test, which are dealt verified in population and not particularly Lucknow population, but this is what we all get as a kids.

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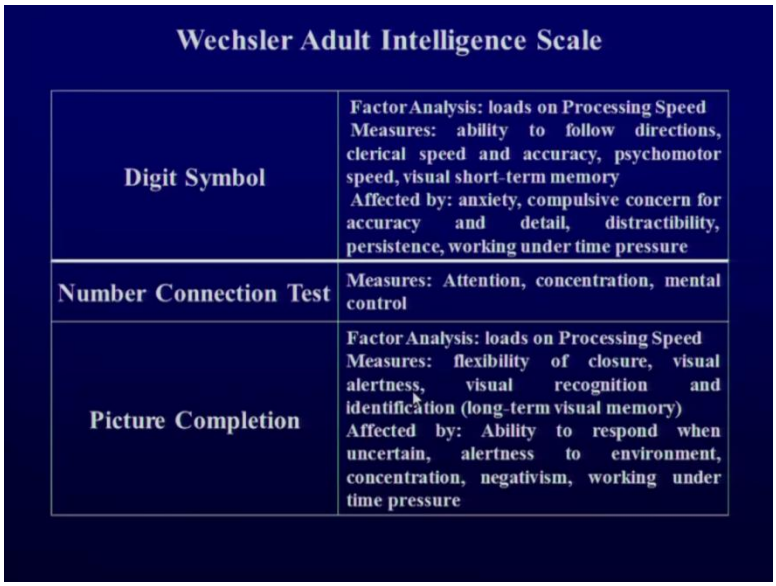

And this is what we done the digital symbol of the number connection and the picture complexion.

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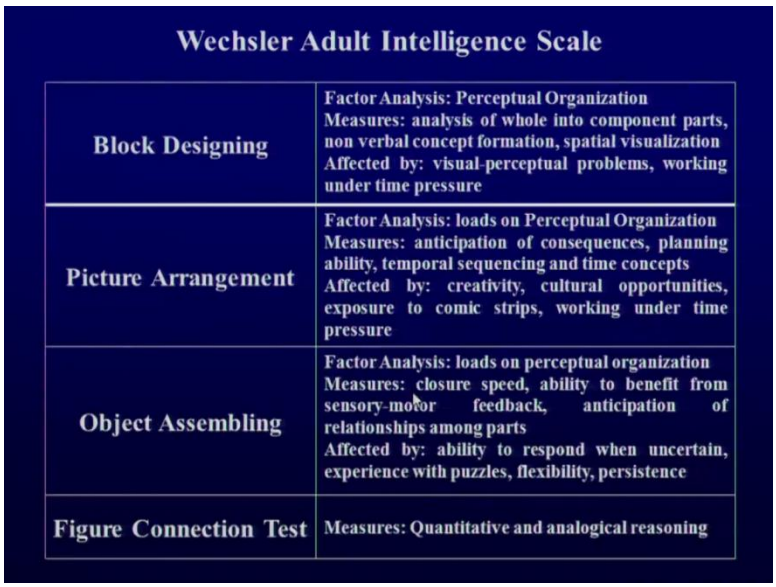

Block design picture arrangement objects assembling figure connection and the figure connection designed by us.

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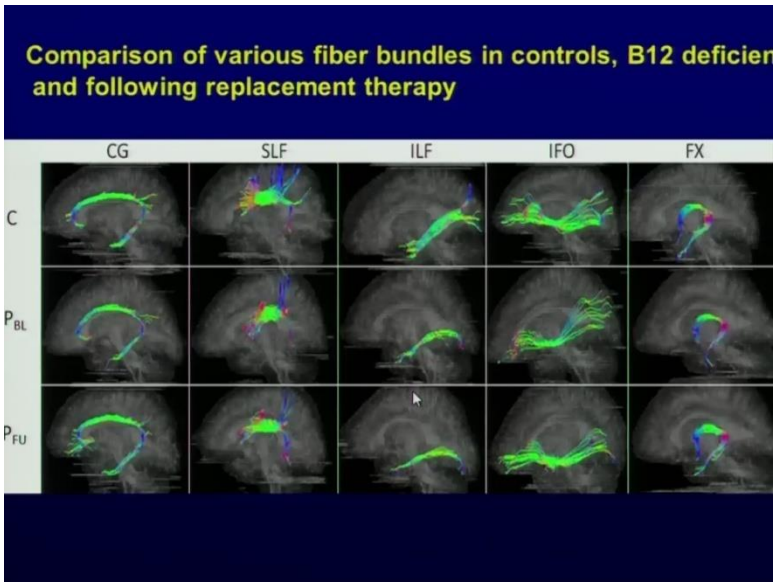

Because the number connection upon which is used for people who are educated you know one two three four. But the figure connection is the one which is used for un educated who are illustrate when I joined h p g I there was a guy called of nayak who was interested with the medical thapolopathy and he converted the number connection into the figure connection test validated large population in the healthy population as well as the hypothetical sound of the population and we now this is assigned to tell accept it worldwide.

In a people who are not educated who can read the things and that is where the test we gave in a now this is one example. So, this is the method of tractography which was designed by doctor rathod and it is the very, very objective method of segmenting the white matter tracts because if you draw with your hands there will be some kind of subjectivity and their producebility will not be there. So, I was telling you all the time that I will not accept any task which has subjectivity if I total fibres extra I will get the higher efficient value if I get two fiber get lesser value. So, there he came out with the automatic segmentation method by which you could segment the just click the area and the whole fibres comes out where two clicks the whole fibres connect in a whole. So, that is contribution which he has made to the d t I he has formulate he is the first author of all the technical people.

He published lot of the clinical problem by the along with it. So, this method gives you all the single f s l f I l f I f o and the fornix. So, beautifully shown and this is what we are trying to show is in the patients who are b twelve deficiency and they are been treated and then they has he. So, this is a group patients who was had a b twelve deficiency proven b twelve deficiency on most still was high was high the b twelve the b twelve deficiency means the b twelve has to be low even if the m m e of b twelve if the m m e is low when the b twelve is low we are still normal in near or may not be there, but b twelve definite way to say b twelve deficiency. So, what we did was just compare the data of different fibre bundles available which we could do by the natos method of tractography and we could actually see look at the look at the motor fibres.

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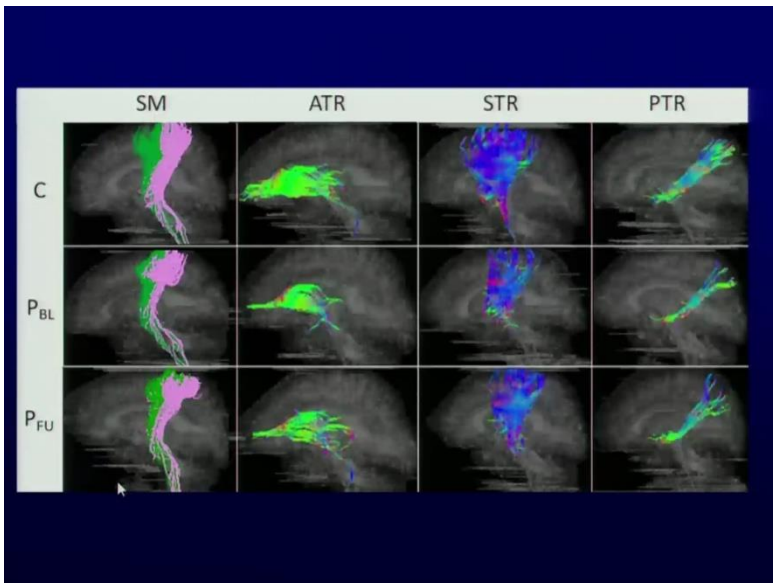

And this look at this motor fibres and that is sensory fibres very nicely you can see the different colours a t r p t r s t r in the different in the in the healthy and when I use a word healthy very interesting these I will talk about here see I always believe that a people we all in the lever healthy even me were healthy. So, I think this can do mine that someone vegetarians and someone non vegetarians. So, why not you do the b twelve because we were in the hospital where they have start a day free excess to the b twelve level without paying anything. So, all the staff members who are coming to us for this test as volunteer. So, we decided to do the b twelve and homocysteine levels and we were surprised a quite a good number of people had a b twelve deficiency. So, that we would

be realise that we should not take the individual healthy be of some they are healthy on the clinical examination they should be, because if the cognition.

Is not picked up the final cognition like the has to something which we do they are like fine testing they are like the gross water gross you know this intelligent I q or something you know which is we have see abnormally we can say well they had said normal on the gross course which you do that mini-mental function tours or something. So, they are not the one which are having the fine changes that is what is important actually in terms of cognition in this individuals. So, I decided to draw those those patients in the list I did not do further analysis of those patient I was concentrating on the patient and the control who are having normal b twelve that became definition for me to take the normal b twelve. So, these controls of extremely b twelve normal. So, that is the one I want to empathize here and that might give me an idea that we discussed in the last today's with doctor bharath bhooshan that something which is going on.

We do not know what is going with us and once the guy is having a poor mms mmsc or poor iq. So, you do not have to do a rocket science to define them right only when there is the fine changes in the cognition is like mathematical skills for example, just like to give you an example. So, that is way of difference may common have you do not know I mean you have to you guys have to do all these things to design those kind of methodologies to how if you do that.

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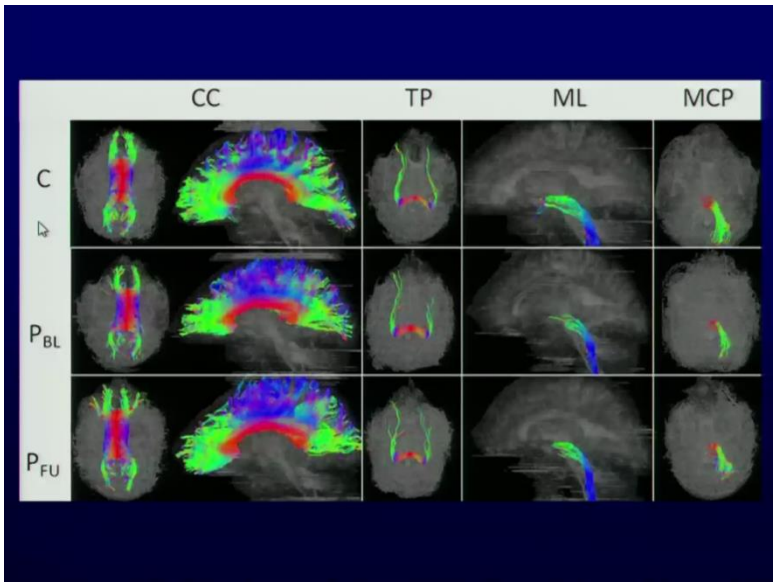

Now, this the close up just click things every things comes under this, this is all beautifully you know tapetum memory sky m c p and when we quantified.

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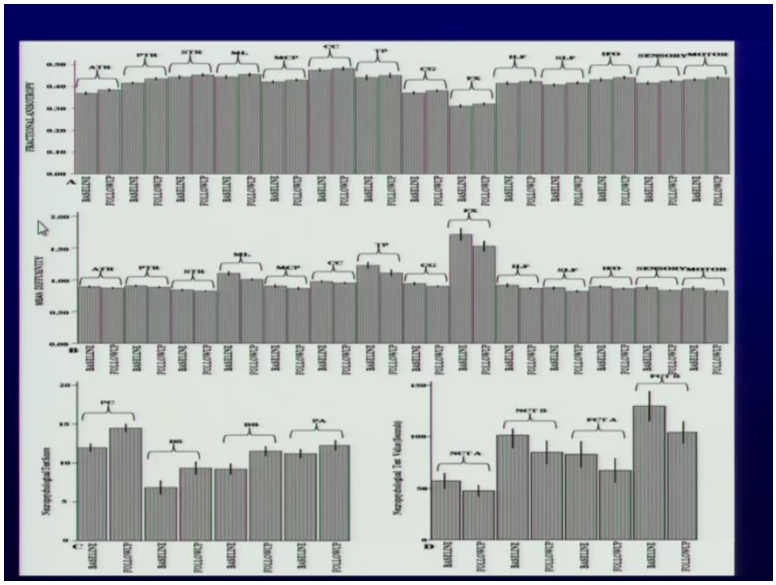

What we found was you could see the significant changes you know in the different fibres I want to say a subreddit dislodge and there are two main cells we do in the dti which is I think you should be interested not only in the MRI, but tractography as a psychologist because if you have a good light and there is a wall in between then you cannot see the light coming through right. So, I think the message has to be conveyed through the tracts whatever function you are trying was this and I think that is we has the role of if the hand is on movement what function going to assess right, then we will do perceive moment this movement that movement that is not a collateral motor movement. So, the bundles are defected right the conduction is not there. So, I think for a psychologist my request is look at the tracts also do not think the f MRI is the next in the word and try to develop a connect on theory like connecting the function and in the wires together because you can have a good power coming in, but there is no wire is short the light is on going to. So, I think wire is not import to the source of light.

So, that is what I want to do convey its very very important message and if you look at this what we are finding is there are changes in all the tracts most of the tracts suggesting there by b twelve is a disease or what we call is effecting the central node system the spinal cord be manifest first, but changes are in all the white matters as you can see from

this in this in all and study that m d in f a r which are major of this things, and they are and look at the neuropsychiatric test, these are the test which are abnormal in this individual symbol this is surprising you know that you have changes which are; obviously, abnormal.

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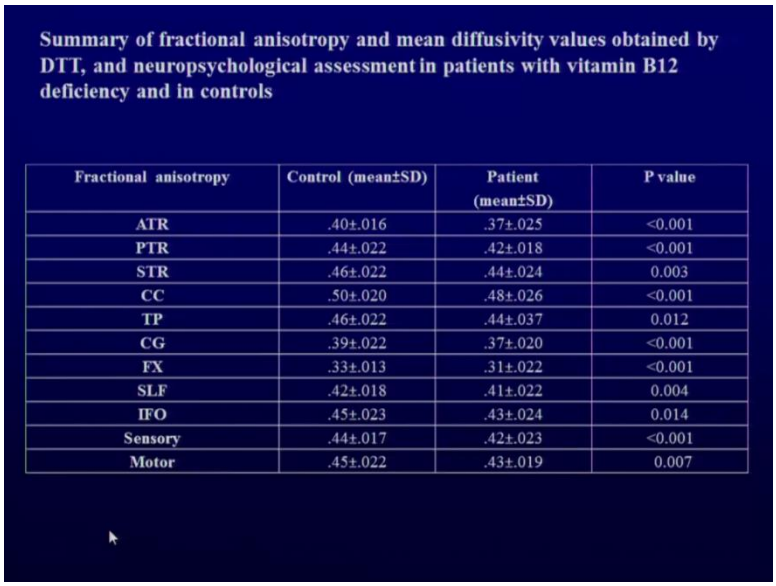

And these are the numbers which clearly show the significant difference you know if you look at this all the tags they are showing. So, disease is not confined to like posterior column of the spinal cord it is because it should not be. Why should a particular segment be when there is defect in myelination or it is affecting the myelination it should affect the whole myelination of the brain in the system. So, that is what we are trying to prove this has not been done earlier that is not very excited about the study we have taken adult population, and we have taken the cognition adult population b twelve level and not only see the spinalcord we have seen the breath which is normal looking on a machine.

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Mean Diffusivity			
PTR	.88±.026	.90±.036	0.017
ML	.99±.068	1.10±.097	<0.001
MCP	.86±.039	.90±.080	0.004
CC	.93±.035	.97±.050	<0.001
TP	.99±.085	1.25±.187	<0.001
FX	1.45±.19	1.70±.28	<0.001
ILF	.83±.030	.91±.081	<0.001
SLF	.82±.042	.87±.098	0.010
IFO	.86±.030	.89±.052	0.001
Sensory	.82±.020	.88±.10	0.003
Motor	.81±.021	.86±.095	0.013
Neuropsychological Test			
PC	14.94±1.39	12.20±1.64	<0.001
DS	11.25±2.26	7.03±2.65	<0.001
BD	12.78±1.29	9.16±2.19	<0.001
PA	13.22±1.04	11.47±1.97	<0.001
OA	11.25±1.16	9.72±2.04	<0.001
NCT A	38.12±9.23	57.75±22.68	<0.001
NCT B	69.19±15.80	103.97±44.29	<0.001
FCT A	60.25±23.62	80.84±38.51	0.012
FCT B	81.34±25.59	127.56±42.29	<0.001

So, this is the very, very significant study, and one of who's ever I have shown world widely very exited you know I think should put the best channel on something in this what I m working over that you need to know that.

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Summary of fractional anisotropy and mean diffusivity values obtained by DTT, and neuropsychological assessment in patients with vitamin B12 deficiency, at baseline and at follow-up

Fractional anisotropy	Baseline (mean±SD)	Follow-up (mean±SD)	P value
ATR	.37±.023	.39±.020	<0.001
PTR	.42±.016	.44±.021	<0.001
STR	.44±.026	.45±.023	<0.001
ML	.44±.030	.46±.031	<0.001
MCP	.42±.018	.43±.017	<0.001
CC	.476±.028	.483±.029	<0.001
TP	.442±.038	.451±.037	<0.001
CG	.371±.021	.382±.020	<0.001
FX	.311±.023	.321±.021	<0.001
ILF	.415±.027	.423±.025	<0.001
SLF	.408±.021	.417±.019	<0.001
IFO	.432±.025	.442±.023	<0.001
Sensory	.416±.024	.425±.021	<0.001
Motor	.432±.018	.442±.019	<0.001

Now, this is another example of now look at the little side you know pc ds bd, all are showing gross changes you know in this now this is interesting thing from the point of view of that reinforce therapy.

You find the changes are reversing you can see that this is pre and the post in the different fire bundles changes are seen is in the diffusion diffusivity, and the neuropsychological changes are reversing it means the these guys apparently are not normal the apparently with their re leads are not normal in cognition and which can be reconfirmed by the micro structural change in the brain that is what I m trying to say. So, we quantified the area which is usually affecting by the b twelve and the function, which are connected through the wires those you find out.

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Summary of the significant correlations between Neuropsychological Test and DTI measures (Fractional Anisotropy and Mean Diffusivity)

Fractional Anisotropy		PC	DS	BD	PA	OA	NCTA	NCTB	FCTA	FCTB
ATR	*R*	.274	.305	.210	--	--	--	-.329	-.220	-.244
	P	.009	.003	.045	*NS*	*NS*	*NS*	.001	.036	.020
PTR	*R*	.311	.381	.276	--	--	-.221	--	--	-.232
	P	.003	<.001	.008	*NS*	*NS*	.036	*NS*	*NS*	.027
STR	*R*	--	--	--	--	--	--	-.236	--	-.218
	P	*NS*	*NS*	*NS*	*NS*	*NS*	*NS*	.024	*NS*	.038
ML	*R*	.373	.470	.383	.249	--	-.383	-.279	-.309	-.322
	P	<.001	<.001	<.001	.017	*NS*	<.001	.007	.003	.002
MCP	*R*	.223	.302	.240	.244	--	--	-.221	--	--
	P	.034	.004	.022	.020	*NS*	*NS*	.035	*NS*	*NS*
CC	*R*	.219	.386	.321	--	.253	-.313	-.426	-.253	-.258
	P	.037	<.001	.002	*NS*	.015	.003	<.001	.016	.014
TP	*R*	--	.276	--	--	--	-.251	-.298	--	-.220
	P	*NS*	.008	*NS*	*NS*	*NS*	.016	.004	*NS*	.036
CG	*R*	.262	.310	--	--	.270	--	-.287	--	--
	P	.012	.003	*NS*	*NS*	.010	*NS*	.006	*NS*	*NS*
FX	*R*	.308	.374	.303	--	.268	--	-.343	-.252	-.240
	P	.003	<.001	.003	*NS*	.010	*NS*	.001	.016	.022
ILF	*R*	--	.309	--	--	.235	--	--	-.234	
	P	*NS*	.003	*NS*	*NS*	.025	*NS*	*NS*	.026	*NS*
SLF	*R*	.253	.341	.247	--	--	-.376	-.335	-.277	-.246
	P	.016	.001	.018	*NS*	*NS*	<.001	.001	.008	.019
Sensory	*R*	.361	.522	.526	.334	.307	-.441	-.440	-.358	-.484
	P	<.001	<.001	<.001	.001	.003	<.001	<.001	<.001	<.001
Motor	*R*	.314	.375	.309	--	--	-.346	-.407	-.358	-.353
	P	.002	<.001	.003	*NS*	*NS*	.001	<.001	<.001	.001

So, this is a kind of correlation we have we have seen in the some of the test, you can see here show significant correlation and all with the over standard fibres over standard fibres showing the significant changes you know.

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Mean Diffusivity		PC	DS	BD	PA	OA	NCTA	NCTB	FCTA	FCTB
PTR	*R*	-.250	-.298	-.254	--	--	.250	.224	--	--
	P	.017	.004	.015	*NS*	*NS*	.017	.033	*NS*	*NS*
ML	*R*	-.468	-.511	-.409	-.208	--	.478	.341	.308	.459
	P	<.001	<.001	<.001	.048	*NS*	<.001	.001	.003	<.001
MCP	*R*	-.333	-.245	-.379	--	--	.395	.347	.367	.310
	P	.001	.019	<.001	*NS*	*NS*	<.001	.001	<.001	.003
CC	*R*	-.243	-.273	-.241	--	-.255	.282	.344	.219	.254
	P	.020	.009	.021	*NS*	.015	.007	.001	.037	.015
TP	*R*	-.250	-.313	-.340	--	-.267	.441	.350	--	.387
	P	.017	.002	.001	*NS*	.011	<.001	.001	*NS*	<.001
FX	*R*	-.267	-.254	-.213	--	-.266	.274	.314	.232	.314
	P	.011	.015	.042	*NS*	.011	.008	.002	.027	.002
ILF	*R*	-.310	-.312	-.293	--	-.284	.382	.211	--	.304
	P	.003	.003	.005	*NS*	.006	<.001	.045	*NS*	.003
SLF	*R*	-.238	--	--	--	--	.293	--	--	--
	P	.023	*NS*	*NS*	*NS*	*NS*	.005	*NS*	*NS*	*NS*
IFO	*R*	--	-.218	--	--	--	.273	.295	--	.244
	P	*NS*	.038	*NS*	*NS*	*NS*	.009	.005	*NS*	.020
Sensory	*R*	--	-.283	--	--	--	--	--	--	--
	P	*NS*	.007	*NS*	*NS*	*NS*	*NS*	*NS*	*NS*	*NS*
Motor	*R*	-.207	-.275	--	-.214	--	--	--	--	--
	P	.049	.008	*NS*	.042	*NS*	*NS*	*NS*	*NS*	*NS*

There are huge number of fibres and some of the them are differently showing the significant changes

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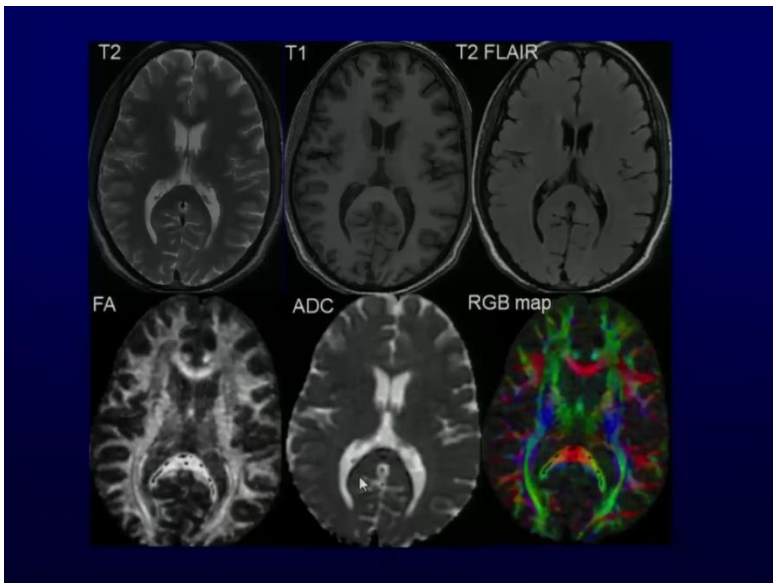

Now, that is how a brain looks like on imaging if you look at this brain is a per perfect looking brain on t two and if you look at the dti maps as that they do not show any gross changes unless we quantify, and if you quantify by putting the dts in interesting a b or c and all these things it is very cumbersome and we do not know which all fibres are affected. So, I think that is where we use that methodology of quantifying the bundles

rather than quantifying the reason of interest actually get to whole bundle out of the difference and we hypothesise that we should have a defect in myelination affective all the fibres only one or three fibres.

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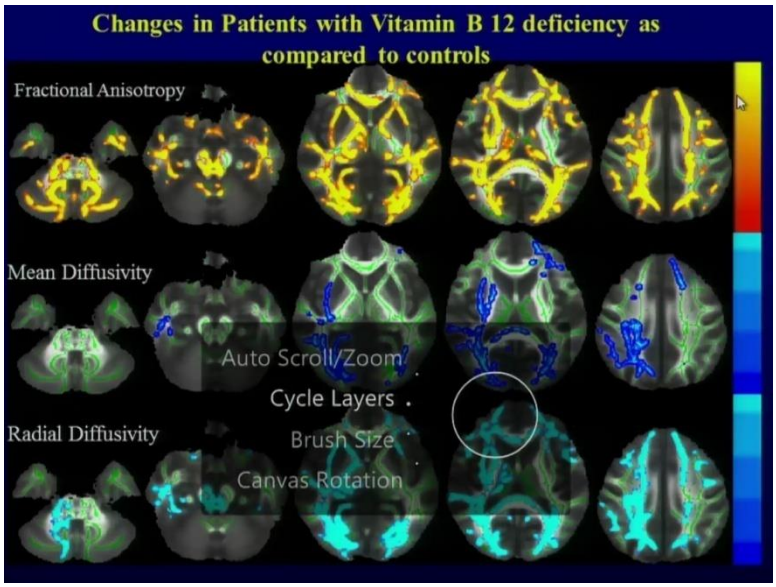

Now, this is the one which I wanted to share with you this data is based on about fifty five patents where we have used technology where we use the efecelikly do magistration emilie template whatever I talk to you yesterday this is absolutely done use the vbm analysis and everything has been done in this methodology is as per the design of the west, but patent belongs to India, but design is west and what is interesting you find is this is the t b s s tract based spatial statistical analysis the green are the green thing which was seen are the structure which are the fiber structure that is how they defined the green area which was seeing is fiber define structures now the yellow area that the one which are significantly different from the control. So, you can see how much white matter is different you know from the control look at the cerebellum look at the mid brain. So, wherever the white matter is there it is.

Clearly showing abnormality this is important now I think you can draw your own conclusion is it the cortex which is important for an inner cognition or it is the white matter also is important I am not sure you really guys are bother about the white matter and more you only bother about the cortex. So, another message which I am trying to give. So, this methodology is that the white matter is as important as the cortex and if

you look at the cortex is the difference of very obvious and this is the highest significance the yellow represents the maximum differences which are observed and red represents the lower part in all the significance goes down as the function of colour this look at those look at the similar fibres I mean this is unbelievable callosum which I which you mention in the tractography the same fibres are actually seen even with tractography still if you say well you clicked it you write the note rothod was wrong he dint do the right kind of tractography.

So, all contestants can be done, but even by an alternative method we have find the similar results what we find in. So, that shows the power of the methodology being used by rathod we see his standard method used worldwide and it confines to the hypothesis we have the myelination defect is a irrespective of the area of the brain and it has relationship with the professionality of the brain that is what you want to convey now this is another method we we use and if you look at the changes in the fu which is the much sensitive measure of the fiber bundles then the md mean diffusivity and the mean diffusivity is wont is showing the similar changes in some of the area like this area is temporal area is confining temporal area here and look at the external capsule external capsule is here the oxipural traits oxipural traits here.

Some of the oxipural traits here this is interesting and what is interesting is radial diffusivity see here we did the radial and the axial diffusivity also there are number of parameters you can take to understand the micro structure change in the brain and the radial diffusivity was defiantly showing much closer relationship there, if I if you look at this has compare to the main diffusivity. So, you can just see that a normal looking brain on conventional mri even in the conventional dti can be unrewarding and how this methodology is these are independent methodology methodologies we are not anything we are not putting anything extra here and there is an automatic approach forty brains these are fifty seven brains data and forty seven controls this is not a small number. So, how beautifully you can demonstrate the changes in different fiber bundles using different methodologies I mean that is that is important.

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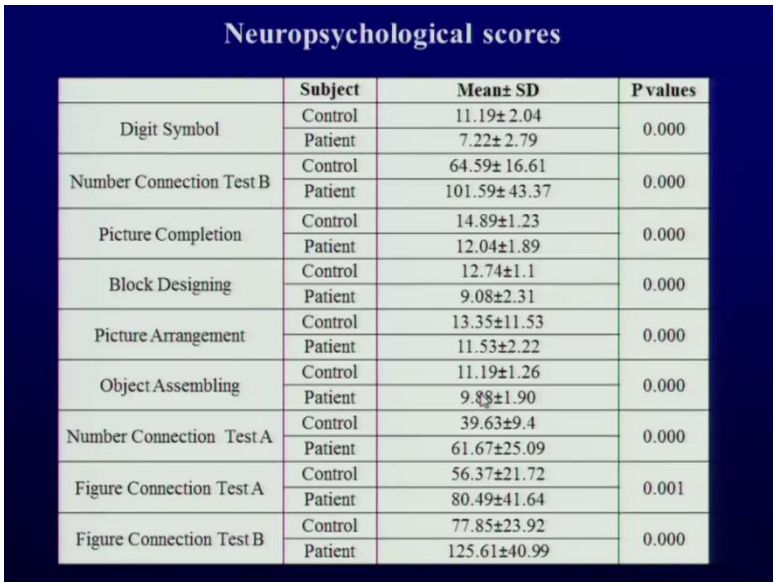

	Subject	Mean± SD	P values
Digit Symbol	Control	11.19± 2.04	0.000
	Patient	7.22± 2.79	
Number Connection Test B	Control	64.59± 16.61	0.000
	Patient	101.59± 43.37	
Picture Completion	Control	14.89±1.23	0.000
	Patient	12.04±1.89	
Block Designing	Control	12.74±1.1	0.000
	Patient	9.08±2.31	
Picture Arrangement	Control	13.35±11.53	0.000
	Patient	11.53±2.22	
Object Assembling	Control	11.19±1.26	0.000
	Patient	9.88±1.90	
Number Connection Test A	Control	39.63±9.4	0.000
	Patient	61.67±25.09	
Figure Connection Test A	Control	56.37±21.72	0.001
	Patient	80.49±41.64	
Figure Connection Test B	Control	77.85±23.92	0.000
	Patient	125.61±40.99	

And if you just look at the neuropsych in the same group innovation like this is another one group this is another group actually and we find the digit symbol number connection and picture complain all are showing changes you can see that p values are different the cortex is because this study can design the cortex as well as as white matter it is a white matter bundle which is affected this and we know from the basic science at the how the b twelve affects the brain function. So, it matching with what has been talked about fifty years back hundred years back it conforms to that what we have say and it shows the cognition defect around is there they are pretty interesting

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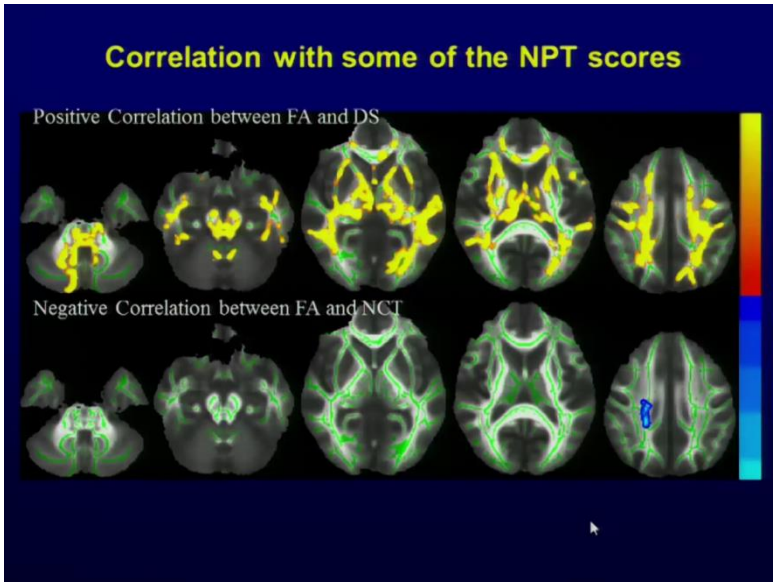

Now, than we did the correlation studies now this is on e way of doing the correlation now today with the f s l methods you could actually put your cognition test. And define the area which say which we are the cognition correlation is coming significant correlation and look at the fa and ds with digit symbol that showed correlation is in number of areas in the brain can you see that paris time temporal lobes cerebellum cingulum the frontal white matter external capsule occipital area. So, that is a kind of relationship that the digit symbol had with this. So, you can define the the your areas you know on the brain directly. So, this methodology. So, you do not have to guess from which area is connective descrimine for the particular test. So, there is something I would liked about this and this is very powerful because very powerful in terms understanding the psychology we seen as now when we looked at the correlation with the f u with the n city these are two types which is showing to correlation we did we tried three or four.

We dint try all of these we will take a lot of time it takes about two to three days to do each each analysis high computation method is required, and you could see this is the area the cingulum area showing you the negative correlation with a f a the number connection test in the referral I would show in that this is combining the control and the and the patent together.

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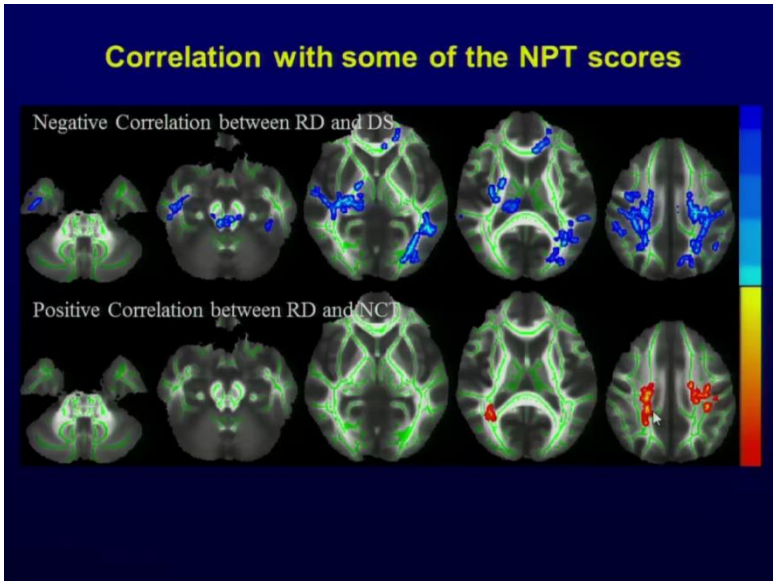

Now, this is looking at the correlation between the at the npt and the rd the negative correlation of radial diffusivity of the ds and you can say similarly ready what I want to showed you update like lets they has extinguishing what we are saying the changes which has seeing in the r d value is compared to the f u in a similar correlations are seen in the similar areas. So, look at the look at the reproduction the correlation and look the reproduction and whole thing which we are seeing here in this now possibly.

In the r d and the city these are the two areas cingulum which we can see and the part of this occipital as whole or the alter area, which is showing you some changes and these are the green colour show the traits.

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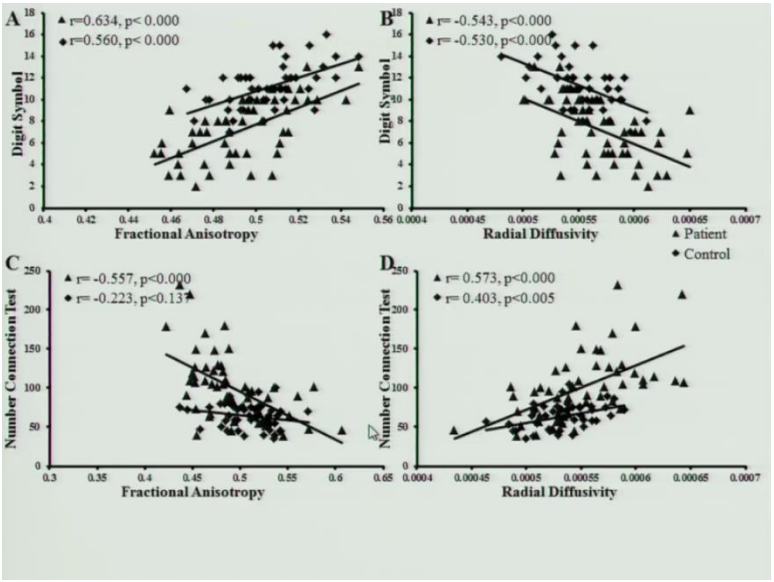

And then we what we did was we tried to get those numbers out for the regions and tried to look on the correlation with the digit symbol and with radial diffusivity exactly same there was you say and there is actually which you have seen the numbers of as they coming out correctly what you are saying except in this particular thing the triangle is patent in this thing I was finding that the control is out showing the relationship, but patent sees older relationship the triangle. So, what I am trying to say is that you go back and forth you do r o analysis of same we have gained you find changes.

So, you just take the global picture put the arrival individual patent from the same region and again you find the changes over there. So, you can always conform, but any methodology it is there it is not a false it is not a something it is coming from some

where it is not a just a mathematical chance you got this it is actually there that is what is important. So, that is why took us two to four months to the regress analysis lobe because when we had a somebody coming from u s we said oh why do not to check the r o s and see whether they are correct or not it would be double you show what is there everybody want to say have a and he wants to be show what is what we are talking about and it turned to be right it is a very extensive kind of exercise is about its worse doing it because it gives you answers. So, this is a part of the story.

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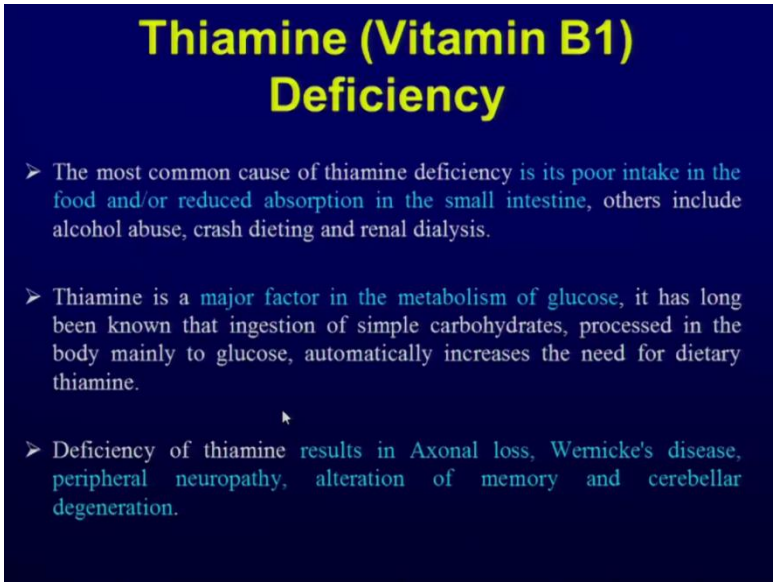

I wanted to cover with you with respect to the b twelve I think this is something we should be the futuristic we have to understand how the b twelve that the the technology may not be available to you at this point in time in in the field.

But the proof of the technologies is the proof of the concept is there in terms of technology neuropsyc verses micro structural change the plane that is what you say difficult and b twelve is something which is not uncommon to have a deficiency I think about thirty to forty percent population they say what do you see not even the people though is for. So, you see huge population which may be neglected and like calcium calcium in the vitamin d same way is the b twelve is the one with has not possible. So, moving quickly to another area which interest over selves. So, the time it is again as common as that if you look at literatures thiamine just common as b twelve may more common, but when you only know from the history the wernicke psychosis karkaroff

psychosis and you know the marchiafava bignami syndrome there are two thing you know which has seen in the only one thing left eye we have.

Now, we all know the thiamine deficiency sheet why became interested in solved way that that is the reason for that when we were working on thiamine deficiency lot of work in thiamine deficiency I happened to spend some time in usually and my student who was also a student of lot over Rajesh and he showed me the data of the after day sleep apnea he wanted to look at the data from the radiologist point of view do you have any changes in the the brain in this before they write a paper actually. So, they want the validation of the normality of the brain here typically done by all basic scientist. So, I was looking at the data I said well I do not find happy with the mammillary body they do not know size then they are some normal in size and I just pointed out number of times yah I think this some normal this not normal this not normal look besides. So, he told to supervisor who are the very well known neuro scientist.

Is that any doubt doctor gupta said very fine that and he decided to develop a software methodology and quantify the volume of mammillary body objectively rather subjectively and when as he found there was significant difference in the volume of the person they control he got very excited and we had a paper in I think neuro report or I think we had a paper on neuro report on this I do not remember exactly I was a one of the carotene he put me the goutham or I picked as the finding exactly. So, he had no reason to not into keep me in that paper and he put that. So, then I realise why not look at our patents of the hepatic encephalopathy who were known oncoloc synopsis oncolic we all know we know they will thymus. So, you give thymine. So, no issue of that and that was a genesis of this whole work see I started from somewhere else.

How I went to look at the thiamine and ours people are the first people in the world actually with this by the way I should tell you that now we know the most common thiamine deficiency is a poor intake in the food reduce the absorption small bow l including alcohol abuse crash dieting and inner dialysis these are the standard methods available for thiamine deficiencies patent with kidney failure and dialysis we do it crash course in dieting, because they have their own method of you know with this it is a major factor in the metabolism of glucose known that injection of simple carbohydrate processed in the body mainly to glucose automatically increase the need for dietary thiamine deficiency of thiamine dissolves in axonal loss wernicke's disease peripheral

neuropathy alteration of memory in the cerebellar degeneration this you know from where wernicke's encephalopathy or wernicke korsakoff syndrome you know which is histological proven one everybody has shown histology and all this in the guys who described their names have this they showed the histology on this. In fact, they had a big debate with one of the groups actually I was in spain giving a talk on this. So, they were pretty exited very critical also as usually know look everything findings are alone

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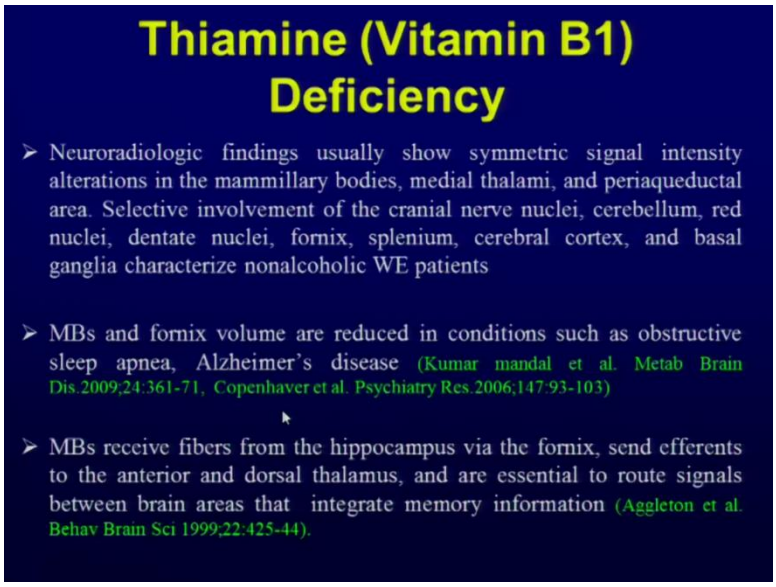

If you see them they are there you can say that yes they are there then no problem with that alteration in the signal intensity mammillary body the medial thalami periaqueductal area and selective involvement of the cranial nerve cerebellum red nuclei dentate nuclei fornix splenium cerebral cortex and the basal ganglia and they characterize non-alcoholic this is what they say non-alcoholic wernicke's encephalopathy syndrome I had a patent actually who came from gorakhpur she was a medico she was the gynaecologist.

She had I think something like for one week she continuously doing deliveries you know she had. So, many deliveries in nursing home she dint take her meal properly and she came in coma to king george medical college with an MRI, and then she brought the MRI to me as a look like a wernicke's encephalopathy and then it will be to MRI my place and I say well looks like vornix do not look like je je is very common that area and je does not affect the memmilary body I usually say definitely looks like wernicke's encephalopathy she was given what I mean one b one and next day it is a third day I saw

her then same boy and called at with girl as how is your wife yeah she is there. So, that is that is the kind of response you know if you are aware of the methodology. If you are aware of the condition and you can become disease there is a difference she the girl the women was in coma she was standing next to he when I asked how is your wife he is oh she is fine we give her syman she got up.

So, that the kind of response you guys what I am trying to say it is an important deficiency it can call haven to your life and it can be diversity. So, I think it is important for us too m b and fornix volumes are reduced in conditions such as obstructive sleep apnea with because this is the paper from kumar and metabolic this is paper revolves mandal metabolic disease and sleep apnea and alzheimer's this is what they have showen alzheimer's everything has been imperial them because we do not know what is alzheimer's. So, we say everything was alzheimer's right b twelve b one b six calcium everything is what have been indeed everything is abnormal in this row mb receives fibres from the hippocampus via the formix send efferents to the anterior and dorsal thalamus and are essential to route the signal between the brain area and integrate memory functions. So, I mean this is what the this is from the brain.

Behavioural sciences the importance of this apparatus hipocripal apparatus that is very important for the memory and you know cognition we all know that right and thiamine affects that MRI.

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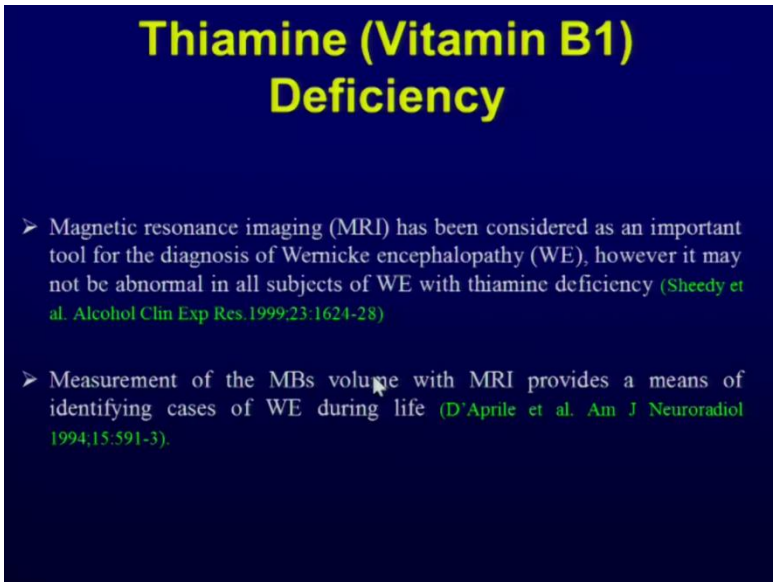

If you have wernicke's encephalopathy yes it is a good tool it can tell you, but every patent does not have wernicke’s encephalopathy; however, it is not abnormal in all subjects of wernicke encephalopathy thiamine deficiency you know if you see its fine we do not see without fine that is what the problem you know the measurement of memmulary body with the MRI provides a means of identifying the case of wernicke during the life, if it is it is not easy to define wernicke encephalopathy in the absence of quantifying the volume of the memmalary body or signatureates memmalary body this was been combined by this guys from radiology.

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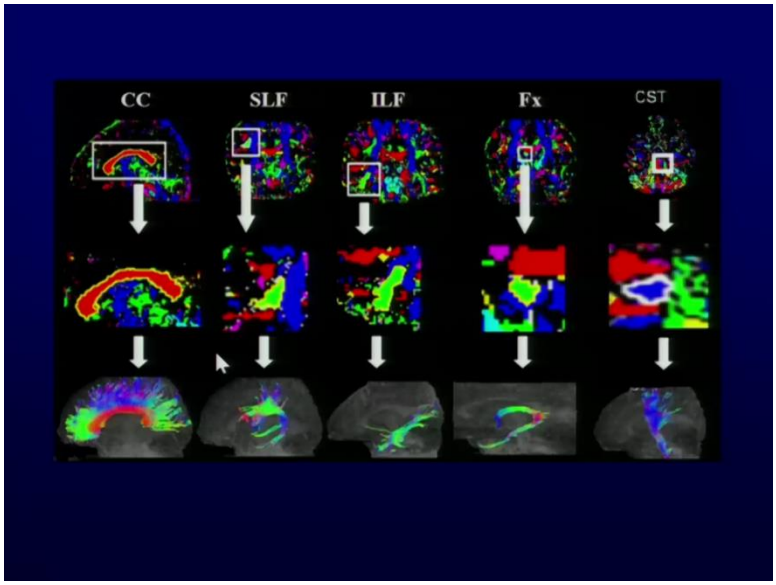

Now, this is the method I was telling with raw to develop segmenting automatically the fibres.

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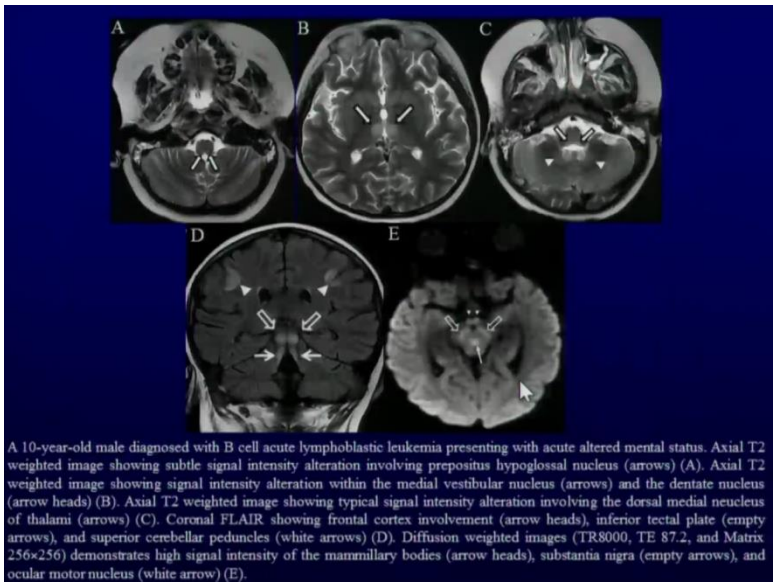

A 10-year-old male diagnosed with B cell acute lymphoblastic leukemia presenting with acute altered mental status. Axial T2 weighted image showing subtle signal intensity alteration involving prepositus hypoglossal nucleus (arrows) (A). Axial T2 weighted image showing signal intensity alteration within the medial vestibular nucleus (arrows) and the dentate nucleus (arrow heads) (B). Axial T2 weighted image showing typical signal intensity alteration involving the dorsal medial neucleus of thalami (arrows) (C). Coronal FLAIR showing frontal cortex involvement (arrow heads), inferior tectal plate (empty arrows), and superior cerebellar peduncles (white arrows) (D). Diffusion weighted images (TR8000, TE 87.2, and Matrix 256×256) demonstrates high signal intensity of the mammillary bodies (arrow heads), substantia nigra (empty arrows), and ocular motor nucleus (white arrow) (E).

And this is what typically the vornix you know the cortical involved and memmalray body involvement the thiamine the middle thalimine involvement very classical the points, we see pantries involvement very classic.

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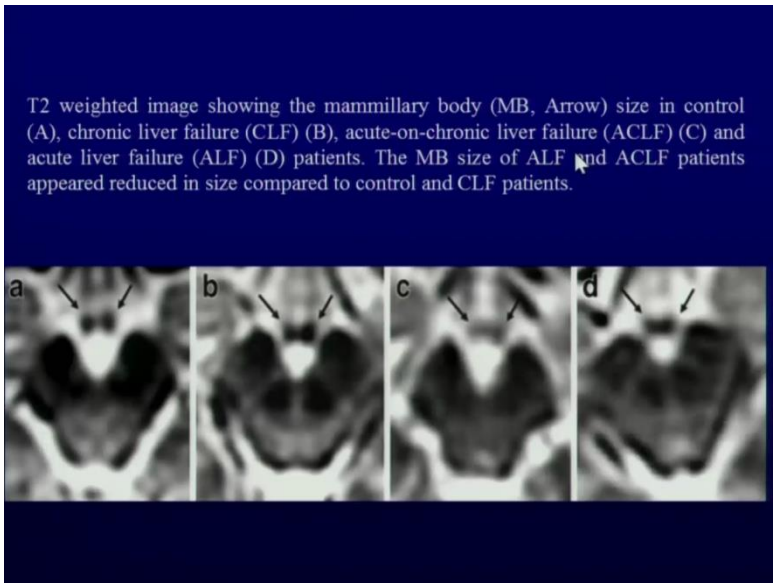

Vornix of this is what we did we took took the patent of acute liver failure of it was say acute liver failure acute on chronicle liver failure and controls and this is the control and very interesting aclf alf and as you go down this is the one, we show in the maximum reduction size of the mammillary body and the chronic liver failure. So, we had a control

chronic liver failure acute liver failure and acute or chronic liver failure. So, acute liver failure is one which called the suddenly reduction the size of the memmullary body not the chronic in a patent who is not alcoholic synoptics this is all ignore alcoholic and what we did was we actually did the tractography.

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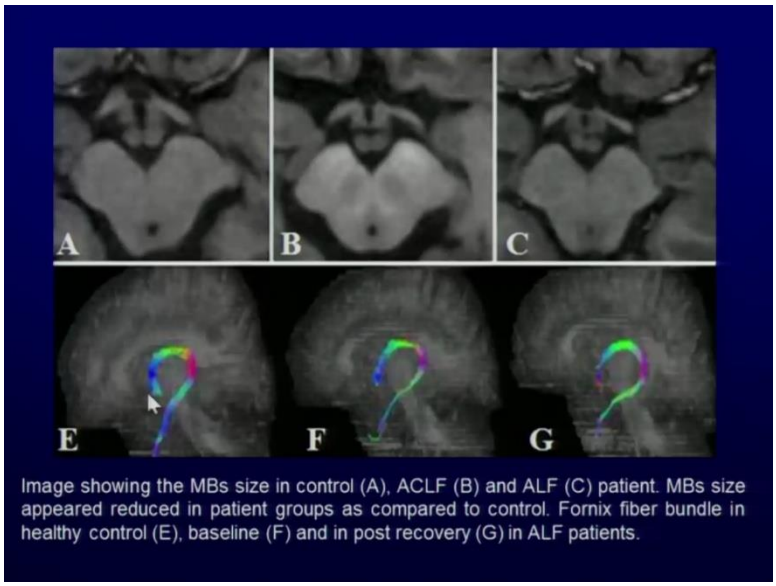

Look at the folics in control aclf and the alf that the folics bundle and we quantified the thiamine labels in the controls acf and alfalf showed the alf is the one.

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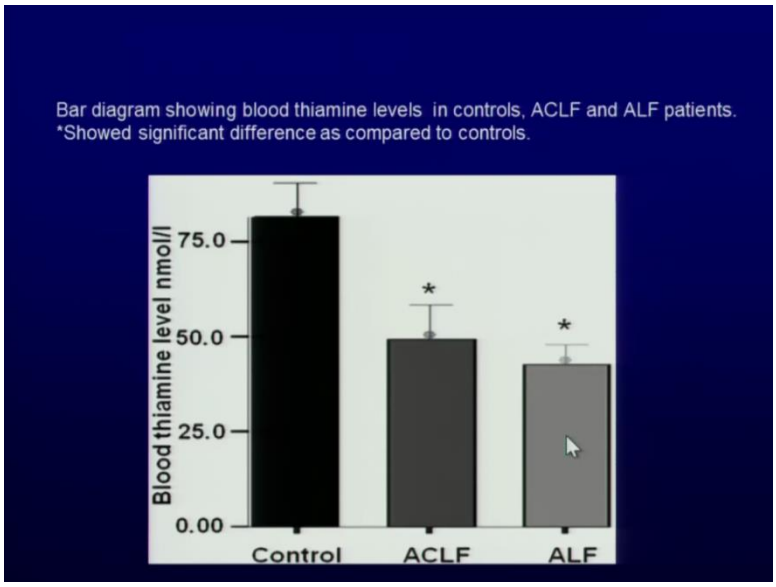

You know what is alf is acute liver failure the person develops a sudden loss of the liver volume, because of acute infection the liver like a like hepatitis hepatitis a hepatitis a is the one which has commonly caused the liver shrinking, but sometimes the b has even causes the sudden shrinking the liver c does not caused that function and which is very common as the rain starts coming Kanpur you know the worst area of liver disease liver failure because of water contamination.

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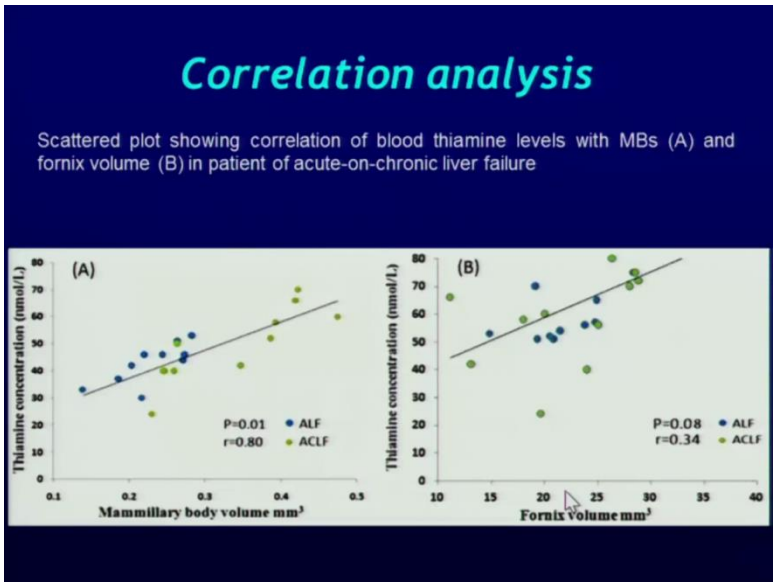

And look at the thiamine concentration in the memmellary body volume relationship the fhonix volume and the thiamine relationship and more beautiful in the alf.

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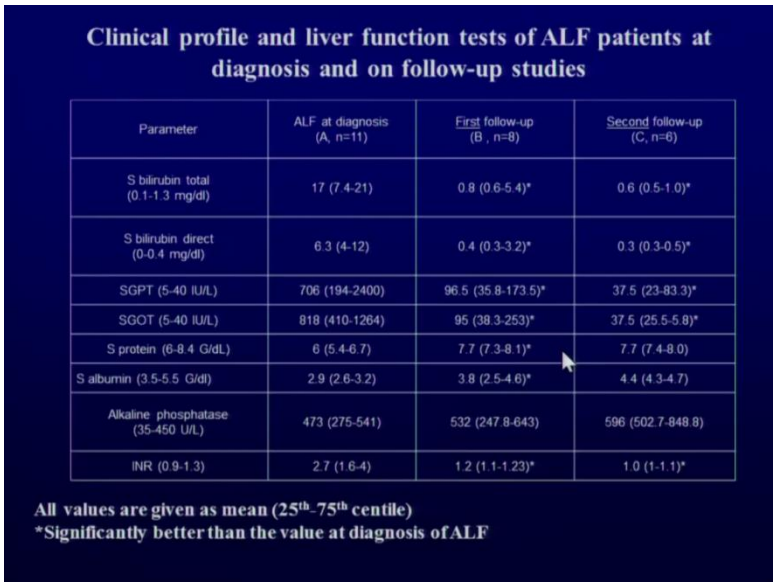

And this is look at the alf and aclf both are there, but you can see the difference in them and this is interesting story about children wired children, who actually come for acute liver failure they are though question of vercol they are like ten years eight years nine years you know and this is a profile at the diagnosis time and the follow up and the second follow up we follow this patent till six months. And if we look at the liver as in they are absolutely normal they become more or less you know perfect, but they still suffer from abnormalities continues of the complimentary.

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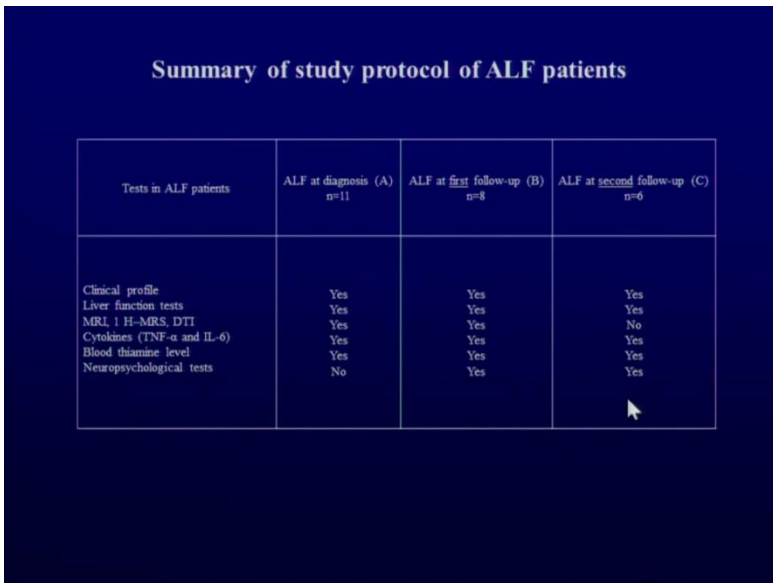

Now, this was the clinical profile this is what all we did this patents is always published actually.

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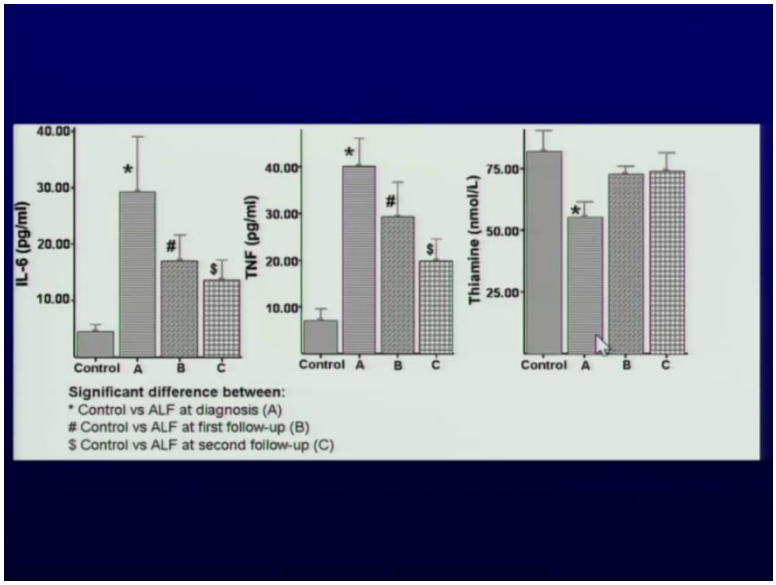

And we quantify the il six the I mean suducoins cimucoins il six tnf alpha and the thiamine levels in all this controls and and you as is recovered the thiamine level improves now liver is a very interesting point why liver shrink you should call the thiamine deficiency the patent you see in coma the liver shrinks very quickly we together do not supplementing thiamine whether the guy do not eating anything is sufficient the food if you take a food sufficiently and you do not supplement thiamine while the patent is in coma. So, the liver stores quickly declines and that is why this declining the thiamine is a.

As the liver biggest to come back the thiamine biggest to come back the more or less story is in you must in inject thiamine over here even the liver is going down the thiamine level should be there you know to maybe...

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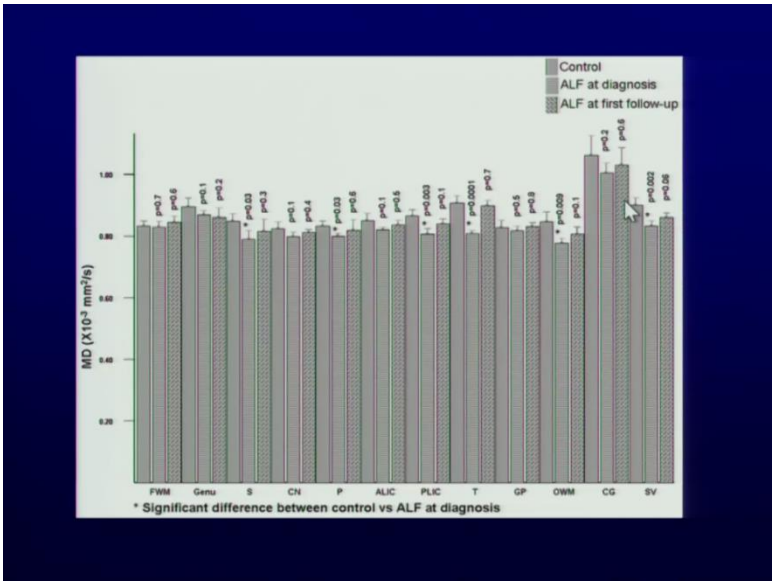

That is a reason that to improve the functionality of mutual run at later date. So, this is main difference between values in all the regions this is c s values and this is neuropsychological test look at the neuropsyc test first trying we could nubruco pressure rather than coma as he recover at six week, that is where six week and these are six months look at the recovery even though it was old register normality in terms of here, but child has recovered and you can see that the relationship of this is population already this work.

So, what I am trying to tell you towards is how important this small small you know things all like thiamine b twelve calcium people do not care and for a normal individual in the medical terminology I call it is the person can walk he can eat he can talk he is normal, but that not true there is much more to normal than what we see and this is what all we see. So, I think this is what we should the moral of story is that this is not something uncommon this is seen wherever we are and I think if you can help this guy by getting the b complex or thiamine or calcium you know nutrition supplements. So, that is we are it is going to make a better colony of convection and better colony of life to the individuals I think this is all what I want to say about the vitamin deficiencies and the cognition you know and it is important sir thing here basically in the hospital experiments and the staff most called.

We found that in many of the apparent normal population there was deficiency of in the returns. So, is it not possible that when across their entire population some of us might be deficient in at least some aspect of nutrition some children. So, why not I mean do we have general profiling of all the individuals and then see the impact of - you see I will give you very interesting story if you go to the us you find that the you find every material food in need a supplementary you know with iron with b twelve with b one and all the kind of things you know supplementation is there in this country the supplementation is only there for the iodine this is by a law because of lot of human cry was made by all Indian medical sciences conducting huge number of studies kucchupalli and he showed that iodine.

Is important like mental tardation and you know must be in knowing on gorakhpur area was a one which was very huge belt for iron deficiency in gaiter and it became a law and it became like you everybody heard as salt you know you here in this people and the tv also you know, but somehow these are not been taken as seriously neither by the nutritionist nor by psychologist and we do not come into picture I am by mistake I am doing this because not answer. So, I have nobody in the picture my interest was in nutrition point of view its I come from the country which is deficient in nutrition you can see a lot of kaposi whatever they call it in hindi you know melitition is there in this country and this is the part of mallitation what we are handling.

So, the quality of human beings are dependent on the quality of food they take it may not be in terms of like berger or something it may be standard roti in daal and chawal, but it should be have good supplementation they should have proper food and that is what they require to make them good human beings good means good in interact good in functions see we want population we should be good in intelation function I am not sure where the caminals come from which may ground and what they rosome thing that is another story you can think about why certain people have you know different frenter lobe than the other guys is the nutrition or something we do not know about that nobody has done this nobody thought about this it seems, but this is one area I think I totally good point to excide the psychologist to get into this area and you understand why we have been rather than going into typical adsd this there were debative it is standard care practice care you know in new psychology and that was does not giving anything.

What gives you importance is if you can define this problems any population and dissolve this population problems and may be create in the next five ten years a legislation supplementation of vitamin b twelve thiamine this is what we require in this country, I am the odd man to talk about we call the radiologist I am not a clinician not nutrition, I am not a psychologist I cannot talk about this I can only give you what I can do the proof of concept the rest you have to take forward and of us I have a data actually in this study as on a connectivity which I have not analysed fc the functional inductity. So, I was to grind actually of a connectom and b twelve this is what I am tiring to trying to propose then if you can do connectable b twelve and that is the way to go actually.

And get to understand how this whole thing you know and I will be happy if you could be a part of us and we could involve you whether the part of our study of course, lot of will there you could also be part of a study where you could at least ask you to provide us the right kind of test which you should perform in this patent you want to design some interest for us and that is where it is important to and I will certainly put you one other co co-investigater of the study which we are trying to get from invidious forum and its important it is a in this country nobody talks about this everyone talks about standard na who clear about the skit the fate you know ocd you know you know the standards which you have been doing courageous you know talk something different you know which you which you and me had not heard about.

And I am sure more psychologist do not think about b twelve or b one - little different thing my explanation I mean one thing that you are focusing is man nutrition why not it also be than that living in an polluted city for a long period I mean even that may be have an impact on your cooperative functions for the extremely …….where you see the polluted city you know I have this one to say orcinic is one which is known to afraid to build function let is other one own build function, but if you look at the blood levels of orcinic they are not in high for example, in kanpur they are not high in luknow there small area in luknow there we had some orcinic problem issues whether florine is high this is orcinic is also high some areas you know.

In unnav, but that is all, but b twelve is something which is like you know pollution in general if air pollution if you are saying its water pollution air pollution all these are important and how the air pollution is effecting the brain I cannot say anything about it point with this something I will level I can show that you know it effect the respiratory

function if we talk about the air pollution, but certainly not talk about the brain function, but this has the proven track record of the aniline synthesis and this is mailonic varman and carbo hydropretabism brain function these are strategic things you know which we are talking about which we know from where hundred years story of histology brain atapsy brain function those you know we have know all things, but now this is the way to prove that this has to way to prove that something we are not we are reendowing it we are not saying it we had wanted it. We are we visiting the area which was told by our forefathers you know what happens I am not doing something different only thing I am rediscovering the same story in a different fashion, that is all I am talking about and make sense.