THE PROCEEDINGS OF THE FIFTH ANNUAL INTERNATIONAL NEUROSURGERY CONFERENCE

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The Annual Conference of the:

- NEUROLOGICAL SURGERY RESEARCH LISTSERV
- SKULL-BASE-SURGERY LISTSERV
- FUNCTIONAL AND STEREOTACTIC NEUROSURGERY LISTSERV
- SPINE LISTSERV
- PAEDIATRIC NEUROSURGERY LISTSERV
- NEUROTRAUMA LISTSERV
- NEURO-ONCOLOGY LISTSERV

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Neurosurgery in Syria

Hani Meniawi MD

Question

Question 1

In the early history of Syria, during the golden days of Islamic Caliphates,what kind of neurosurgical procedures were performed?

Do you have some evidence if ancient craniectomies were performed, for example, skulls with signs of ancient craniectomy; from which era or year, and what were the indications?

Question 2

How many public hospital are in Syria, and which ones are performing neurosurgical interventions?

Question 3

What is the proportion of neurosurgeons in relation to the population of Syria?

Thanks in advance

Leonidas M Quintana MD

Answer

Dear Dr.Quintana,

Thank you for your questions, I forwarded your questions to my freind Dr.Jalal Najjar who is writing detailed study about the medicine in ancient islamic days.

The numbers of public hospitals in Syria: I do not have precise statistics but, there is at least one public hospital in every city with over 30 000 population, in major cities like Damascus, Aleppo, Homs, Latakia etc.

There are many public hospitals covering all medical services, most services are free of charge, but recently the patients are requested to contribute a fraction of the costs.

The number of neurosurgeons are about 200 for 20 millions population which makes the proportion about 1/100 000.

Thank you very much or your questions

Hani Meniawi MD

Comment

Dear friends

thank you for such important questions and I think I can help with the first one.

Before a thousand years, during the Islamic era a huge number of scholars were practicing Medicine and undertook surgery and also dissected cadavers.

As the controlling power was the islamic Caliphat, there was the same level of civilization and Medicine in Damascus, Baghdad, Andalus, because it was all one state.

Albucasis was a pioneer in surgery and his non-sinking skull perforator was the first in the world to avoid laceration of the dura. He also invented the Anaesthetic sponge.

For the first time, the last chapter of his book 'Altasreef' (called iron work or hand work), more than 200 photos of surgical instruments and the way to use them were described including ligation of blood vessels and cat gut for internal suturing.

Ibn Nafees was famous in cadaver dissection and said what we see by anatomy is something different of what we read in old books, so he disagreed in many points with Galen.

Rhazess had great famous book discussing Galen Medicine and phylosophy.

Avicenna, or Ibn Sina, (980-1037) described making a cranial incision and the way to

avoid eyelid nerves injury. He also described the biomechanical features of the vertebra and the spine almost perfectly. For example he had described that the anterior longitudinal ligament is stronger than the posterior ligament because anterior movement is needed more than posterior movements.

In their books you can also find great details about neuroanatomy, spine treatment (spine truma, kyphosis, spinal tuberculosis), neuro operations, hydrcephalus, and surgery for migrain by cautery.

This is a really great subject and needs more than article or book to explain the level of Medicine during the Islamic era and civilization. I hope I have highlighted few of the important points.

Jalal Najjar MD

Spine surgery and evidence base
General discussion

Comment

Dear Colleagues:
Does Evidence Based Medicine methodology apply to neurosurgery? This is the real question to consider.

Gordon Smith, past editor of British Medical Journal addressed this issue very well when he did systematic review of the literature regarding the use of parachutes in airplanes. Here is the conclusions of his review “As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomized controlled trials. Advocates of evidence based medicine have criticized the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organized and participated in a double blind, randomized, placebo controlled, crossover trial of the parachute”.

If you need the full reference of the paper here it is "Smith GCS, Pell JP. Hazardous journey Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomized controlled trials. BMJ 2003;327:1459-1461."

If we apply evidence based medicine methodology we should ban parachutes in planes, seatbelts in cars, do not remove extradural hematomas etc as they do not have the evidence to support them and they cost us a lot of money.

Craft based specialities like ours do not lend itself to double blind randomized placebo controlled crossover trials "the holly grail" of evidence based medicine except when it comes to using medications e.g. steroids, anticonvulsants, antibiotics etc, but not any thing involving cutting, insertion, stimulation etc. In these circumstances we can randomize between two different treatments or techniques if the surgeons felt that they were in equipoise. The results of this method however can not and should not be applied to all patients suffering from the same illness, e.g. we have seen the ISAT trial being applied to every aneurysm, but the trial only recruited a handful of eligible patients, similarly the STICH trail was negative because of intention to treat analysis, analyzing patients who had surgery as if they did not, similar findings affected the results of the SPORT trail.

Surgeons need to take stop, take deep breath and think before jumping onto the bandwagon of evidence based medicine, perhaps what we need is evidence based surgery, which is different and requires different methodology; we all know that what works in somebody's hands may not work in another's hands. Could it be the we need the null hypothesis seeking trial in surgery.

May I thank all the contributors of this conference and big 2010 cheers to Naren for organizing and moderating another excellent conference.

Sam Eljamel
MBBCh, MD, FRCSI, FRCSE, FRCS(SN), FABI

Comment

This is a very respectable discussion. However, evidence based studies are not absolute, and has its own limitations. Literature cannot be interpreted in the absence of common sense and clinical experience. Therefore, just because a treatment is not supported by high-quality medical evidence does not mean that a treatment has no value.

On the other hand, the Cochrane group only considers randomized controlled studies as valid sources of medical evidence. The absence of such studies, in their opinion, equates with the absence of evidence. This can not be applied to every study, especially

those under common sense. Lastly, what is the case in newly developed techniques and prosthesis with no literature stores. Would their early studies be a crime!! There is no doubt that hidden agendas made the background of the picture hazy, dark, and offensive. However, fear and doubt should never stop noble ideas and true studies, upon which a good number of data will be collected for later evidence-based conclusions.

At the end, I would like to stress that evidences and conclusions have short life span as the evidence based evaluation process to reach the (best guess solution) is under strict guidelines; of which (periodic UPDATE) is mandatory...ie., what is strong evidence now may turn weak later on.

Thanks

Mohamed Mohi Eldin , MB-BCh , M.Sc., MD

Comment

Dear Dr. Narenthiran:

I completly agree with Dr Fink regarding excessive indication of complex surgery for treating cervical and bck pain. In Brazil there is the same tendency.

Despite I'm not being a spine surgeon, I believe that there is few or no indication for surgical treatment of axial pain and for those who not exhibit neurological symptons and signs.

Thank you very much.

Benedicto Oscar Colli MD

Comment

Dear Naren,
I am a spine surgeon and about 80% of my operations are mainly spinal cases. In response to Dr. Fink observation, there is no doubt that doctors are under huge pressure from medical companies to adapt some procedures or to use some devices; the decision making process of surgeons becomes more difficult with the amount of publications defending this or that device, looking in depth , many magazines or authors are having some interest or financial benifits in talking for certain devices.

The introduction of spinal instrumentations made it possible to help more patients with problems seen 25 years ago as untreatable, like adult degenerative scoliosis, but it is unfotunate that the number of spinal fixation is mounting in a pathological curve and in many cases without proper indication and the basic rule of proper clinical assessment and finding the source of pain and not least the proper correlation between all this and the imaging studies are simply not followed.

Thank you for putting this issue for discussion.

Hani Meniawi MD

Comment

Dear Dr. Fink,

I am agree with you in respect that there is a current tendency of over use of procedures for fixation, fusion and instrumentation for many spinal pathologies that before were treated with less complicated approaches.

In an evidence medical based point of view a lot of these procedures are unnecessary.

A review of the literature about this theme have shown that for example in USA between 1996-2001 the surgical spinal fusion increased by 77% compared to 13-14% for knee artroplasty, The main costs of each procedures is almost $ 34 000. The business of spinal implants or prothesis is around 2000 million of dollars/year. However the results with this techniques aren´t better.

There is a strong correlation between the increased use of complex spinal surgical procedures and the low scientific evidence supporting their use. This is currently a worldwide problem.

In my opinion the indication of lumbar fusion in lumbar degenerative spinal disease is only in ísthmic spondylolisthesis that refractory to medical treatment and in degenerative spondylolisthesis with spinal stenosis of low lumbar spine.

The procedures of spinal fixation have increased their indications too and, in some cases are used prophylacticaly to avoid the reoperation for instability or post laminectomy pain while the instrumentation runs the risk of increasing the morbidity and the rate of reoperation.

It would become incumbent for us to undertake long term randomized controlled trials to obtain the evidence we need to decide on the best treatment in our patients with degenerative spinal diseases.

However, the number of prospective randomized clinical trials performed in surgery is much lower than the number performed in non-surgical settings. The design of this type of trial in surgical patients carries an additional set of difficulties on top of those predictable in any clinical trial. The opportunity and validity of the methodology for patient randomization, techniques and, most importantly, surgeons is still highly controversial. The classical methodology for the design of prospective randomized clinical trials must be substantially modified to adapt to the special requirements of clinical research in surgery. On the other hand, the randomized prospective clinical trial is by no means the only source of clinical evidence and in many instances is either unnecessary or plainly harmful.

1. Deyo RA, Nachemson A, Mirza SK. Spinal fusion surgery. The case for restraint. N Engl J Med 2004; 350: 722-726.

2. Delgado Lopez PD, Rodríguez Salazar A, Castilla Díez JM, Martín Velasco V, Fernández Arconada O. Papel de la cirugía en la enfermedad degenerativa espinal. Análisis de revisiones sistemáticas sobre tratamientos quirúrgicos y conservadores desde el punto de vista de la medicina basada en evidencias.Neurocirugia 2005; 16:142-157.

With best regards.

Angel J Lacerda MD PhD.

Nanotechnology in neuromodulation

Russell Andrews MD FACS

Question

Congratulations for such a wonderful presentation!!!!

I am mainly dedicated to vascular neurosurgery, and my first question for you is:

1) The by-pass surgery, using STA-MCA is a very old technique to improve the collateral CBF, for potential or actual regional cerebral ischemia. But, sometimes the time to suture with Ethilon™ 10/0 , 12-notches around the borders of anastomosing arteries, takes too long (in trained hands 30 to 40 minutes).

How could the nanotechnology improve this technique, shortening the time for the by pass be patent, using “The Gecko Effect”, you showed in your wonderful presentation.

Have you tried some nanotechnique for this vascular theoretical cases?

2) In the future, I agree with you that endovascular techniques will be so much developed than now, but according to my present thinking, of course limited, we would have to perforate the capilar arterial or venous wall to lodge some nanotechnological elements. How you tried experimental research introducing any such techniques?

Leonidas M Quintana MD

Answer

Dear Professor Quintana,

Thank you for your insightful questions - which I think might be considered the ‘inside’ and ‘outside’ aspects of the same issue: "How can we attach the microvessel wall atraumatically?"

Certainly ‘Gecko tape’ could be tried for vascular anastomoses - likely someone has already done so in the lab but, I am not aware of it yet. And on the 'inside' aspect - we will naturally be interested in attaching micron-sized electrodes to the appropriate spots inside the capillaries. "Nanohooks" can no doubt be fabricated to do this - but to perforate the capillary wall (e.g. for drug delivery) is more problematic.

I am attaching an article which is quite ‘eye-opening’ with regard to nano-assembly. Self-assembling amino acid solutions can form nano-scaffolds that can not only guide regenerating axons, but can also be an amazing hemostatic agent. Google 'Rutledge Ellis-Behnke' for some fascinating papers (his email at MIT is given in the attached paper). I look forward to seeing you again soon!

Russell Andrews MD FACS

Question

Thanks for agreeing to participate in this conference and I am looking forwards to your lecture. Nano-electrodes precisely implanted in the target have huge potential in tailoring neurostimulation to each disease entity and each patient. How close are we to apply this technology? Do we have a prototype that can be tried in a clinical setting? How will these particles be activated/controlled? How would power be supplied to these particles?

Sam Eljamel
MBBCh, MD, FRCSI, FRCSE, FRCS(SN), FABI

Answer

Dear Prof Eljamel/Sam -
Nice to hear from you! And thanks for your questions, which I am repeating here for clarity:
“*Nano- electrodes precisely implanted in the target have huge potential in tailoring*

neurostimulation to each disease entity and each patient, how close are we to apply this technology? do we have a prototype that can be tried in a clinical setting? How do these particles are activated/controlled? and how do the power supplied to these particles?"

First - I am including the questions posed by Richard Bucholz, since the responses apply to some of your questions also:

1) It would appear that the most straight forward, and easily realized, application of carbon fiber technology is improving recordings from microelectrodes used during deep brain stimulation lead implantation. What are the barriers to using this technology within the next few years in this specific straight forward application?

Reply: I believe Keefer's work (slide #42 ff) is landmark in this regard. Simple coating of microelectrodes with carbon nanotubes (CNTs) greatly improves both recording and stimulating *in vivo,* as the NASA Ames group and others have shown *in vitro*. I suspect there are two main hurdles to bringing CNT-coated electrodes into clinical practice for DBS:

(1) FDA or CE Mark approval (testing for toxicology, etc)

(2) Industry 'inertia' - a common phenomenon where existing technology which is profitable is retained despite better technology, because the perceived cost (financially) of conversion is too great in the short run. Hopefully a start-up company that fabricates CNT electrodes will not be bought out by one of the large equipment manufacturers only to have the technology 'shelved' in the interest of short-term profit. Neurosurgeons (and physicians in general) working together can do much to educate others (including the equipment manufacturers, the government agencies, and the public) about the advantages of new technologies.

2) What clinical application (for example movement disorder, psychiatric disorder, dementia, etc.) does Dr. Andrews see as the most fertile domain for the initial application of nanotechnology?

Reply: We are currently using dated micro/macro-electrode 'hammers' to strike whatever nervous system disorder appears to be a nail - movement disorders, mood disorders, epilepsy, obesity, *etc*. We have ignored, for the most part, the neurochemical aspect of CNS disorders since our 'hammer' has been electrical. One might consider the conversion of neuromodulation from the present technique to neuronal/glial level 'nano' techniques similar to a conversion of the criminal justice system: one can replace the electric chair with 'social rehabilitation'. Which 'crimes' might respond best is difficult to predict. My interest is in advancing our techniques, since there are many excellent clinical centers ready to try new techniques on a variety of CNS disorders. With that preface - to respond more directly to Dr Bucholz's question, I would guess that refractory epilepsy might be the initial 'success story' for these new techniques - largely because in many instances epilepsy is a relatively well-understood focal abnormality with an electrical 'signature'.

With regard to your questions about how the 'nanoelectrodes' might be activated/controlled, and how the power could be supplied:

I believe the work of Rodolfo Llinas *et al*. on endovascular recording/stimulating (slide 56 ff) using the vascular tree to access anywhere in the CNS, and that of Kendall Lee et al on 'Bluetooth' communication (slide 19 ff) are steps in the right direction. When the power needs become greatly reduced due to more efficient charge transfer, the 'battery' might even be the heat of the human body or the motion of daily activities. And if one's cell phone can be localized with GPS, we certainly should be able to locate electrodes (perhaps dozens or hundreds) by an externals programming device for selective monitoring/modulating or 'recharging'.

Hope the above is of some help - and I look forward to talking with you further!

Russell Andrews MD FACS

Question

Dear Dr Andrews,
Really fascinating evolving technology and research!

Could you possibly give us a timeline about seeing this great research in the realtime operating table as an established application?

Aristotelis Filippidis MD

Answer

Dear Dr Filippidis,
There are many aspects involved. Some might be implemented in the next few years:

-- Stimulation techniques using feedback and/or desynchronizing techniques (e.g. the work of Tass and others - slide 9 ff)
-- Coating existing microelectrodes with carbon nanotubes to dramatically increase record/stim capabilities and decrease power needs (subject to toxicology studies in small and large animals) (e.g. Keefer et al slide 42 ff)
-- Incorporating neurochemical recording (e.g. the work of Lee et al - slide 19 ff)

Other aspects are more likely a decade or so in the future:

-- Using the vascular tree to access any part of the CNS minimally invasively

-- Multisite (dozens or hundreds) record/stim at the cellular or sub-nuclei (small numbers of cells with similar function) level, which would require so type of communication/ feedback among the many micron-sized 'electrodes'.

sBut it is difficult to predict the future - and not just in neurosurgery. In 1960, most of us (except perhaps those like Richard Feynman) probably would not have predicted that 50 yrs later we would still be traveling by air at subsonic speeds, but that neuroimaging would progress from cut-film angiography and pneumoencephalography to functional MRI. Let's hope that science - not politics or short-term economics - is the rate-limiting step.

Thanks for your question!

Russell Andrews MD FACS

Management of Medulloblastoma

Rutka JT, PhD FRCSC FACS

Question

Dear Dr Rutka,

1. Can we predict which tumors are likely to disseminate at this time with the markers available?

2. When will the microarray analysis become part of the staging process for patients?

George Jallo MD

Question

Dear Dr Rutka,

Although treatment strategies may change in the future, extent of surgical resection remains important. Given this fact, what do you believe is the role of technologies such as iMRI to maximise resection in this patient population?

Additionally, would you comment about the role of neurosurgical sub-specialisation and case volumes in regard to paediatric tumour surgery.

cheers

Paul Grundy BM(Hons) MD FRCS(SN)

Comment

Dear Naren,

Prof. Rutka as usual has exceeded all expectations with his seminal review of Medulloblastomas.

It is a truism that to know the fastest way forward in an uncharted land, you need to keep in mind where you have already been, lest you double-back and fail to make progress.

Prof. Rutka opens the subject by illustrating the primordial surgical contributions of Cushing & Bailey, of Patterson and Farr to radiotherapy and later of Packer to chemotherapy.

Nearly 80 years ago, Cushing wrote that, "If we were to expedite progress, then someone from the disciplines of clinical neurology, pathology and surgery had to assume a more comprehensive role".[1]

In the same manuscript Cushing also reminded us of our quadruple responsibility:

1. of making the preoperative diagnosis
2. of conducting the operation
3. of studying the tissues in detail for purposes of classification
4. of following the patient with an unfavorable type of tumour to the end of his story

Great change often comes from passionate leadership, the likes of what Cushing and a few others have shown. We can all agree that Professor Rutka by following Harvey Cushing's advice (of assuming a more comprehensive role) has not only mastered the subject but has freely passed it on to great benefit of us all in Paediatric Neurosurgery.

Questions:

Cancer Stem Cells:

I agree with Prof. Rutka that with a cancer stem cell (CSC), the game may really be up when you think about surgery, chemotherapy or radiotherapy targeting the cluster of dysplastic cells created by the CSC we call tumour. Only an inhibitor of the CSC can realistically stop the cancer, or it will return within weeks to months.

You considered that chemotherapy may be one way forward. There are some examples of how chemotherapy has resulted in an in-

crease in Cancer Stem Cell population probably by setting off signalling that up-regulated CSC production or its release from controlling mechanisms within its environment (also known as the Stem Cell Niche).[i]

Do you foresee a role for the neutralization of CSC regulators as adjuvant to chemotherapy?

An alternative approach has been to interfere with signalling pathways: Wnt, Sonic Hedgehog (SHh), Notch, BMP are just some of these signalling pathways, that determines individual cellular activity by regulating genetic expression. They seem to work together and are critical for embryonic development of tissues, in determining when cells go into meiosis and into mitosis and when cells are capable of self-renewal and when they go down the path of differentiation.

In your presentation you demonstrated how Stem-like cells in brain tumours have been shown to be selectively vulnerable to agents inhibiting signalling pathways.

Disrupting Hedgehog seems to have resulted in dramatic reduction in tumour size in a recent study. However, the tumour returned and it is believed the recurrence was because of the development of Smoothened Mutation Conferring Resistance to the Hedgehog Pathway Inhibitor in Medulloblastoma[ii].

It is known that Notch Signalling Is Critical for the Growth and Survival of Sonic Hedgehog-Induced Medulloblastomas[iii].

Do you see a role for simultaneously targeting multiple signalling pathways rather than a single one?

Epigenetics:
The knowledge that our protein-encoding genes number as much as the ones found in *C. Elegans* (roundworm) genome (~20,000) was quite humbling to many who initially thought of the human genome sequence to have upwards of 100,000 genes. This paltry number however was not sufficient to explain the significant complexity of the human organism and for the transmission of hereditary information other than mere protein synthesis.

The theory is that the genetic code carries much more than the human carbon copy, but also probably the sum of our forefather's experiences and tools for improved survival. This is the "Ghost in our genes". http://www.youtube.com/watch?v=toRIkRa1fYU&feature=related

And how does this memory or ghosts of the past travel in our genetic code? In your presentation you have referred to several mechanisms that have been proposed.

Epigenetic information is mostly stored as methylation of DNA/chromatin. Methylation is a stable epigenetic mark. The assessment of candidate tumor suppressor genes for evidence of promoter hypermethylation has demonstrated that epigenetic events are a significant feature of medulloblastoma development, and has highlighted a series of genes that are epigenetically inactivated in medulloblastomas.

Most notably, epigenetic inactivation of RASSF1A, HIC1, and CASP8 represent the most prevalent gene-specific events described in medulloblastoma to date.

Genomic imprinting is another way to carry this information. Expression of an imprinted gene is determined by parent of origin and only a small number of genes in mammals (~50) are imprinted.

Imprinted genes violate the usual rule of inheritance in that usually both alleles in a heterozygote are equally expressed but imprinted genes are an exception to this rule. Because most imprinted genes are repressed, either the maternal (inherited from the mother) allele is expressed exclusively because

the paternal (inherited from the father) allele is imprinted or vice-versa.

Variable imprinting of H19 (TSG) and IGF2 in foetal cerebellum and medulloblastoma has been noted. Loss of imprinting (biallelic expression) of IGF2 may promote tumour growth. It has been noted in medulloblastomas or medulloblastoma cell lines but can also occur in normal foetal cerebellum.

Do you feel that these are good surrogate markers for medulloblastomas?

Of the several epigenetically Inactivated Genes in Medulloblastoma which do you consider the most likely to be a target for manipulation?

Do you feel that specific restoration of tumour suppressor gene function is a realistic goal?

May I also say that I found the presentation most inspiring and thought-provoking.

Thank you again.

Guirish Solanki MD FRCS(SN)

i. Vasyl Vasko: To Evade Chemotherapy, Some Cancer Cells Mimic Stem Cells. American Association for Cancer Research's second International Conference on Molecular Diagnostics in Cancer Therapeutic Development, September 19, 2007, Atlanta, GA

ii. Robert L. Yauch, Gerrit J. P. Dijkgraaf, Bruno Alicke, Thomas Januario, Christina P. Ahn, Thomas Holcomb, Kanan Pujara, Jeremy Stinson, Christopher A. Callahan, Tracy Tang, J. Fernando Bazan, Zhengyan Kan, Somasekar Seshagiri, Christine L. Hann, Stephen E. Gould, Jennifer A. Low, Charles M. Rudin, Frederic J. de Sauvage, Smoothened Mutation Confers Resistance to a Hedgehog Pathway Inhibitor in Medulloblastoma Science 23 October 2009: Vol. 326. no. 5952, pp. 572 - 574

iii. Andrew R. Hallahan, Joel I. Pritchard, Stacey Hansen, Mark Benson, Jennifer Stoeck, Beryl A. Hatton, Thomas L. Russell, Richard G. Ellenbogen, Irwin D. Bernstein, Phillip A. Beachy and James M. Olson: The SmoA1 Mouse Model Reveals That Notch Signaling Is Critical for the Growth and Survival of Sonic Hedgehog-Induced Medulloblastomas. Cancer Research 64, 7794-7800, November 1, 2004

Neurosurgery and Latin America

Leonidas M Quintana MD

Question

Can you further explicate the roles of various Neurosurgical centers in North America and Europe and Asia in the development of neurosurgical programs in Latin America? For example, numbers of neurosurgeons who trained in different centers outside of Latin America versus numbers who trained within that area?

John Loeser MD

Answer

Thanks Dr.Loeser for this question.

Latin American Neurosurgical Centers at the XXI century are certainly evolving, specially at Mexico, Brasil, Colombia, Argentina and Chile. In this countries we have many neurosurgical center that are technologically advanced, with high level and standards we can find in developed countries, and in this moment they are performing post-graduate training of many neurosurgeons inside Latin America.

However, as happened more than 50 years ago, many young neurosurgeons, in a globalized world, want to learn more, and more, and they continue traveling to USA, Europe and Asia for receiving post-graduate training directly from the "masters".

So, even now in the present time, there are a lot of latinamerican young neurosurgeon that receive special and advanced training in USA,Europe and Asia, mainly Japan.

The number of neurosurgeons that go abroad , to developed countries really I don´t know, but the interesting phenomenon is that almost 80% of the neurosurgeons are receiving a complete training inside the Latinamerican continent.

Leonidas M Quintana MD

Comment

Thank you for your reply. There are complex issues associated with training outside of one's own country. Not the least of these, as seen in the US, is that we have absorbed many, many physicians from developing foreign countries. This is not advantageous to such countries.

John Loeser MD

Question

What strategies can be applied to harmonize the development of neurosurgery in Latin America?

Salazar Moscote MD

Answer

Dr.Moscote Thanks for this important question.

Proposals for teaching methods common to all latinamerican countries, in practice, I see it very difficult.

This is due because ancient latinamerican universities already have programs that have been used for years, and it is very difficult to change this situation.

However, Executive and Administrative Committees of the Latinamerican Federation of Neurosurgical Societies-FLANC, have as a goal, a greater concern in Continuing Education in Neurosurgery, creating opportunities to conduct training centers of excellence in Latin American in the various sub-specialties of neurosurgery, as a way of continuous post-graduate training .

The selected centers have been proposed to develop training programs, for 2 to 3

months, with reduced cost of lodge and food, and once the trained neurosurgeon has finished, he receive a certificate formalized by the FLANC.

Beside from learning, this program is enriched by allowing the exchange of ideas, strengthening cultural ties and latin-american friendship.

The FLANC expected that the experiences of several colleagues have already conducted these stages of improvement, in approved institutions, will stimulate a growing number of latin american neurosurgeons exploit the same opportunities.

Leonidas M Quintana MD

Comment

Comments on the answer of Dr Quintana to Dr Moscote regarding common methods of teaching to all latinoamerican countries;

First of all, I would like to congratulate Dr. Quintana for your nice presentation on the Development of Neurosurgery in Latin America.

I would like also like to comment on the answer of Dr. Quintana to Dr. Moscote regarding common methods of teaching to all latinoamerican countries.

I´m a Brazilian neurosurgeon involved with neurosurgical training during the last 30 years, and currently I´m Coordinator of the Accreditation Committee for Training of Residents of the Brazilian Neurosurgical Society (SBN). Despite my current position, my comments represent my personal opinions only.

I agree that it will be difficult to change the way of training neurosurgeons in ancient latinamerican universities, nevertheless, there are something that can be done.

I believe that to send neurosurgeons for training abroad works well only as a complement after the general training.

Despite Brazil to have almost a half of the area and almost one third of the population of Latin America (third slide of Dr. Quintana), since more than twenty years the SBN is working very hard for improving the training of neurosurgeons in our country. After hard work, some important things were achieved:

1. The SBN has a protocol for accreditation of Centers for Training neurosurgeons that establish the minimal facilities and personal for training and this is periodically checked by the Accreditation Committee. This protocol has been improved and a now a new version is being tested for trying to define what are, in numbers, what amount and kind of surgical procedures the trainees should do for be considered apt to become a neurosurgeon.

2. Every neurosurgeon in training in the Accredited Centers are submitted at least to an annual examination performed by the SBN, and

3. After the end of his training, the neurosurgeon is submitted to a final examination in order to become Board Certified in Neurosurgery.

These are some examples that what can be done. But what happens with the FLANC? It is very well policatilly organized and represent the immediate interest of some neurosurgeons of some countries and unfortunately not very representative of the common neurosurgeons of Latin American countries. Consequently, it has no power for change the *status quo*. Their specific technical committees do not work because they are composed using more political than technical criteria.

I had the opportunity to discuss some of these problems with Dr. Quintana and I believe that he agree with me in many things.
Thank you very much.

Benedicto Oscar Colli MD

Comment

As Dr.Colli says, I agree in almost all the points he stated.

In my comment I mentioned Brasil as a country in Latin America that is one where young neurosurgeons want to receive specialized training. But also, Argentina, Chile, Mexico have their own programs, for the continous training of young neurosurgeons.

I´m not talking about the national post-graduate training inside each country, because this kind of teaching is very typical of each country.

I´m looking for some form of Continous Education Programs, in accredited center of FLANC, for receiving advanced training inside the Latin American continent, a kind of post-title Education.

And, under this point of view, personnaly I think that the Latin American Federation of Neurosurgical Societies(FLANC) has something to say.

I agree that it is a very political and administrative federation, and is under modification of his own by-laws, specially to dedicate its efforts to the Continous Education Programs, inside the continent, and due to the most important reason, that is the majority of our countries are under social-economical development, it´s necessary to prepare our young neurosurgeons inside the Latin American continent. The reason is obvious.

At least, during my presidency of FLANC(2006-2008), more than 40 residents and young neurosurgeons received specialized training in Mexico City, Santiago of Chile, Valparaíso-Chile, Buenos Aires-Argentina, and Brasil, in Porto Alegre, Brasilia, Sao Paulo and Recife. All with excellent comments from the trained neurosurgeons, and teachers of them.

Really I hope this form of specialized training continues inside the Latin American continent because this program is enriched by allowing the exchange of ideas, strengthening cultural ties and latin-american friendship .

This is a very important cultural phenomenon.

Leonidas M Quintana

Comment

I agree with Prof. Quintana that the Continous Education Program promoted by FLANC is an important issue in neurosurgical education in Latin America.

I only want to insist that the basic training (residence) and board certification for neurosurgeons in Latin America should be better evaluated.
Thank you very much.

Benedicto Oscar Colli MD

Question

How the Latinamerican Residents can take part in active collaborations to foment better learning strategies and unification of concepts in LatinAmerica?

Best regards

Carlos Fernando Lozano-Tangua MD

Answer

Dear Dr Carlos Lozano-Tangua. Thanks for your important question. The Latin Ameri-

can Federation of Neurosurgery at this moment is changing its by-laws, to be a more active and agile Society.

One of the proposed modifications is that the Education Committee become directed by a president, who not only coordinates the Chapters of sub-specialities, but also, be engaged in all the aspects of the Education , including Continous Education of youg neurosurgeons and residents; to evaluate and accredit the centers for this training; to have a board helping to evaluate the teaching and learning aspects of the Education, inside the Latin America.

For this reason, we´ll have in the future another Committee or Chapter of Latin American Residents with representative of all the societies that are federated to FLANC.

I hope that these modifications become a reality in the next latin american congress, that will be held in El Salvador, October 2010.

Please, visit the web page www.e-flanc.org
Thanks a lot, and receive my warmest regards

Leonidas M. Quintana MD

Question

It shall be interesting for the Latin-American neurosurgery to publish a book with history of neurosurgery in each of the countries.

Marvin Salgado Perez MD

Answer

Dear Marvin,
The book exists. It was written by Professor Jorge Mendes, the FLANC Historian and published during the Lima CLAN in 2002.

Of course it is necessary to collaborate with him and launch another updated edition.

Leonidas M Quintana MD

Interspinous devices

Mohamed Mohi Eldin MD

Question

I congratulate the authors on their excellent presentation and very good surgical outcome in their patients. You are removing the interspinous ligament and doing foraminal decompression with partial laminotomy. How could you be certain that the improvement seen is the result of interspinous device and not merely due to surgical decompression alone? you really need to do a randomised trial to prove its effectiveness.
regards

Khalid Saeed FRCS(SN)

Answer

Dear Mr Khaled Saeed,

Thank you so much for your contribution. This is an excellent question.

You are absolutely right. However, this early work was aimed to assess the safety and effectiveness on both clinical and radiological perspectives. Other on-going studies are being done to reach other conclusions, including your perfect proposition.

Thanks

Mohamed Mohi Eldin MB BCh MSc MD

Question

Do you always perform the decompression (laminectomy-foraminotomy)? Or do you use the coflex?

What is the difference between coflex and other interspinus devices like: Diam, Wallis, Inspace, X-Stop, ISS?

Thank You,

Antonio Daher MD

Answer

Dear Dr Antonio Daher,

Thank you so much for your contribution. Answering your questions:

1. Spacers may be used alone or in conjunction with surgical decompression, according to the preoperative evaluation of the cases (clinically and radiologically). Some cases with mild stenosis need only the insertion of the spacer, and this would be a very easy piece of work.

2. All spacers have the common advantages of facets unloading, but each of them has its own material and biomechanical structure.

Thanks

Mohamed Mohi Eldin MB BCh MSc MD

Question

Which would be the potential application of the Interlaminar interspinous distraction stabilization device in the facet syndrome?

S Moscote MD

Answer

Dear Dr Moscote,

Thank you for your question. Facet joint pathology may be a cause of low back or neck pain with or without a radiating component. Imaging tests are not that useful for establishing this diagnosis, other than the presence of arthropathy or facet effusions. Diagnosis is often based on exclusion or on confirmation of significant relief after lumbar facet or medial branch blockade. Typical symptoms would include a focal pain over

the facet which is aggravated by lateral bending, extension, and rotation or by maintaining any position for a prolonged period of time. Patients often have point tenderness over that site. Failure of conservative management call for facet unloading, which is the function of the spacers. Also do not forget that degenerative lumbar canal stenosis is primarily a disease of the facets. That why facet unloading is the key of relief in mild to moderate cases.

Mohamed Mohi Eldin MB BCh MSc MD

Question

Very interesting presentation, congratulations!

Just two quick questions:

1) do you have any experience of inserting interspinous devices (not necessarily just Coflex) under local anaesthetic?

2) what is the average length of stay for your patients and do you consider this procedure suitable for day surgery?

Many thanks

Antonio Belli FRCS(SN) MD

Answer

Dear Dr Belli,

Thank you very much for your contribution. As for your questions:

1. the best interspinous process I inserted with local anesthesia is the percutaneous (In-Space) spacer. It is very suitable for old patients with mild to moderate lumbar canal stenosis, not fit for general anesthesia. All other spacers that need surgical incisions can be done under spinal or epidural anesthesia.

2. In-Space is very suitable for day case surgery. Others may need one or two more days.

Mohamed Mohi Eldin MB BCh MSc MD

Comment

Most of spinal surgery can be done under local or spinal anaesthesia. Even laminectomy and spinal fusion. It is surprising how well patients tolerate this.

All interspinous devices can be also placed under local anaesthetic.

I agree for only mild to moderate stenosis as failure rate is high for severe stenosis.

Aprajay Golash FRCS(SN)

Question

Dear Dr Eldin,

Thanks for your good work. Here are some questions....

Do you think Coflex can be compared to Wallis as the latter is claimed to provide stability in extension and flexion as opposed to only in extension with Colfex?

How do you think Coflex, being a midline device might correct segmental scoliosis as shown in Slide 21?

Have you had any experience with erosion on spinous process or a delayed spinous fracture with Coflex?

What are the commonest sizes you employ?

Do you personally believe that preserving the supraspinous ligament provides any significant benefit, anatomically or functionally?

It can be accepted (from your experience and those published) that inserting Coflex might provide some positive clinical benefit of dubious long-term outcome. Do you think that the additional cost burden (in some institutions more expensive that the operation itself) and the need for possibly a lifelong implant would be outweighed by its benefits?

Kind regard

Likhith Alakandy FRCS(SN)

Answer

Dear Dr Likhith Alakandy,

Thank you for your good contribution. Answers to your excellent questions are:

1. The Wallis implant, consisting of an interspinous process spacer that limits extension and two flexion-limiting bands, is intended to improve the stability of the treated intervertebral lumbar segment while preserving its mobility and local lordosis. The same occurs with Coflex that puts the spine in some flexion by its height, and limit it by its metallic nature and closing wings. However, Coflex has the unique advantage of its interlaminar orientation with increased rotational stability, the center of rotation being near to the spinal canal.

2.It is unilateral disc space collapse rather than segmental scoliosis. However, equally distracting the 2 vertebrae based on their spinal midline processes with a midline titanium alloy with its wings adopted to the spinous processes will manage that problem equally on both sides at the treated level, according to the size of the implant.

3. This is an excellent question. It is only published in the Korean literature that some sort of radiological hallow around the wings may be reported in some few cases with the old design of coflex (U-shaped Spacer), representing some form of bony erosion of the spinous processes. This complication was not reported in my series till now. However, recently, after submitting this paper work, one of my new cases, with 4-level microdecompression & 2-consecutive levels of coflex spacer implanted, fell on his back in accidental movement, with temporary LBP that resolved. His follow-up x-rays showed mild tilting of the upper Coflex. It was apparently moved a little. That was a good chance for me to go in again, to see what is going on with Coflex after insertion. I found fracture line of the intervening spinous process between the 2 implants. Coflex devices were very easily removed. I learned many lessons from that case. First, to put 2 consecutive devices, the intervening spine should be strong enough. Second, choosing the proper device size, it should be snugly fit into the space. Lastly, I found it a good SPACER not a FIXATOR. Believe me, despite removal of these 2 implants, I am still sure of its effect when properly indicated.

4. The commonest size used is size 12 followed by size 10, 14, and lastly size 8, consecutively.

5. Preserving the supraspinous ligament, as described by the technique inventors, is one of the key points in keeping the device in place especially in the early postoperative period, until healing occurs. To me, yes, even I try to get piece of the tip of the spinous process with the ligament for later re-alignment.

6. You are absolutely right, one of the corner stones of spine management in general is the cost-benefit issue. It should always be kept in mind during selection of cases. But, do not let it be your glasses during case evaluation. My philosophy is that we should be minimally invasive, keeping or restoring the normal anatomy and function as we can, not biased by any hidden agendas. That way, looking at the MRIs, flashes of the proper modality will shine in your mind. If you have 3 modalities with different selection criteria better or only one modality for all indica-

tions? Choose what is best for the patient as if he is your relative, then comes the issue of cost-benefit. I am sure you will do your best to do what is best for him.

The success philosophy of these new techniques hide in sticking to the proper indications with good case selection, and as I always said, the failure are indication failures most of the time. Because the operation leaves all the anatomical elements intact except for the interspinous ligament, the entire range of other surgical options remains open, including more invasive surgical solutions such as total disc replacement or fusion.

I hope I cleared all your issues.

Thanks

Mohamed Mohi Eldin MB BCh MSc MD

Answer

Dear Dr Ratliff,

These are the answer to your questions:

1. Was the data collected prospectively?

Yes, it is a prospective study, done by me at more than one center in Egypt.

2. Any other exclusion criteria applied ?

Primary exlusion criteria included fixed motor deficit, cauda equina syndrome, frank instability, scoliosis, previous lumbar surgery, significant neuropathy, pathological fracture, severe osteoporosis, morbid obesity, active infections or systemic disease, and vertebral metastasis.

3. what is the plan next ?

The study didnot stop, it is still going on. Our preliminary results were just a step on the road. Moreover, I m trying to collect cases on a national level, and my be some international co-work. This is applied to all my minimally invasive spine interests.

4. Has coronal plan correction been reported with other spacers ?

Yes, but it is frank in (coflex) due to its unique interlaminar orientation.

Looking forward to hear from you.

Thanks

Mohamed Mohi Eldin MB BCh MSc MD

Question

What were the clinical criteria (history and physical examination) used to establish the indications for surgical implantation of the device?

What were the nonsurgical treatments that were used before resorting to surgery?

Was there a patient group who had similar complaints and pre-operative findings who were NOT operated, but who were re-checked at one year?

Was there significant improvement in that group?

Respectfully submitted,

Robert A Fink MD.

Answer

Dear Dr Fink,

Thank you so much for your inquiries. I hope you find the proper answers here.

1. The inclusion criteria were patients at 40 years of age or older with leg, buttock, or groin pain, with or without back pain, that could be relieved during flexion. Neurogenic claudication should be an integral part of the

patient's complaint. Patients had to have completed at least 3-6 months of non-operative treatment, with no improvement. Stenosis was confirmed by CT or MRI scans at one or two levels. Primary exclusion criteria included a fixed motor deficit, cauda equina syndrome, frank instability, previous lumbar surgery, significant peripheral neuropathy, scoliosis, pathological fractures, severe osteoporosis, obesity, active infections, active systemic disease, or vertebral metastasis.

2. a controlled non-surgical group, and a controlled surgical groups are available for consecutive controlled studies under preparation.

Thanks

Mohamed Mohi Eldin MB BCh MSc MD

Regenerating the brain from endogenous stem cells

Ahmed A, Malik, Gray W

Question

To Ahmed et al.:
Thank you for this enlightening review of stem cell therapies that may be used in the future to target central nervous system pathology. Am I correct in concluding from your review that you feel the present emphasis on utilization of fetal stem cell lines is not as promising? Primary clinical approaches to spinal cord injury and cerebrovascular infarcts target limiting secondary injury and aiding functional recovery. Are there any potential approaches targeting manipulation of endogenous stem cell lines? Where do you see stem cells being used clinically in the future?

John Ratliff MD

Answer

Dear Dr Ratliff,

Thank you for your insightful questions.

We think that manipulation of endogenous stem cells are to complement our exogenous attempts (either fetal or adult cells) to repair. There are many reasons why the use of fetal stem cell lines have failed in treatment (e.g.Parkinson's) which include derivation from incompatible hosts, and a probable distance in the differentiation tree. Endogenousprogenitors are probably closer in the differentiation tree compared to those derived foetally and given that there are already in-situ
they are likely to be of greater clinical utility.

Given that we are at a very early stage in this field it is difficult to predict eventual clinical endpoints. There certainly is promise with implanting exogenous stem cells to enhance survival and promote plasticity in the injured brain. This appears to be a non-integrative function on the transplanted cells - in that they appear to produce growth factors that limit secondary damage and promote plasticity but their progeny do not contribute to anatomical repair.

Endogenous stem/progenitor cells have been demonstrated to reconstruct functional circuitry but only under rather unusual (in a clinical context) pathophysiological (mainly apoptotic cell death) conditions. Remyelination in multiple sclerosis may well be an early achievable application but the problem of further damage from the immune system remains.

Best wishes,

Liam Gray PhD FRCS(SN)

Question

Really great and insightful presentation and I think that sheds some hope for the future!

Question 1:

I can understand that the delivery of neural stem cells to stereotactic end points or intrathecal administration (that's a great thought I think) is just the first step in this process. Is a transformation of the delivery microenviroment needed in order to accept the implanted stem cells? Physiology teaches us that a cell interacts with endocrine or paracrine stimulators that alter their function and even lead to cell differentiation. Do you believe that the differentiation of the cells should undergo before implantation or we should leave it to the microenviroment of the implantation?

Question 2:

Are there any reports of stem cell implantation guidance? Meaning that you implant the cells at a specific point and then you guide them pharmacologically or by using their ge-

nome potential to target axon development or implantation sites. This could be of benefit in spinal cord injury I think.

Aristotelis Filippidis MD

Answer

Thank you for your very pertinent questions.

Answer 1:

This is an excellent question and speaks to one the key problems in tissue repair. Transplanting differentiated cells is clinically safer, but they tend to suffer the same fate as the originally injured brain if transplanted early, yet face a hostile remodelled environment if transplanted late. Modulating the tissue response to injury in order to facilitate either direct repair or to facilitate survival and enhance plasticity in the host brain will be key. Simply transplanting cells is the least of our biological problems.

Answer 2:

There have been some reports following stem cells with magnetic nanoparticles on MRI and a few attempts at directing them using externally applied magnetic fields in animal models but I'm not aware of any substantial benefit in doing so. Interestingly, implanted and endogenous stem/progenitor cells seem to be attracted to sites of injury and so this has been less of a problem than originally envisaged. The problem of how to orchestrate functional tissue repair once they get there remains.

Liam Gray PhD FRCS(SN)

ETV in patients with Shunt failure

Essam Elgamal FRCS(SN)

Question

Dear Dr Elgamal,

1.
what was the protcol for management of the ventriculostomy catheter,
i.e height of drain, amount of daily drainage

2.
What was the ICP that was used to diagnosis ETV failure.

3. What do the authors recommend for ETV patients.

George Jallo MD

Answer

Dear Dr George

Thank you for your interest in this paper. The protocol I used was;

- to adjust the hight of the EVD chamber at 15 cm

- The EVD was kept closed postoperatively and continuous ICP monitoring was recorded

- The EVD was only opened for 10 to 15 minutes to drain CSF when the patient is symptomatic of increased ICP that was confirmed by persistently high ICP, then the EVD was closed again.

- Nurses were instructed not to open the EVD if there were no symptoms or signs of increased ICP despite the abnormal recording of high ICP.

- The EVD was removed if the ICP reading remained normal for 24 hours, and the patient was asymptomatic, or insertion of permanent CSF shunt in case of persistent elevation of the ICP even with frequent VSF drainage.

- I noticed that, relatively rapid, rising of ICP after drainage of CSF and closure of the EVD, associated with recurrence of symptomsat was an indication of failure of ETV. It was worse when ICP was 20 mmHg and more.

For ETV I have used this method in a couple of cases when I was not sure about the patency of the ETV, e.g. second membrane surrounded by adhesions, I couldn't get rid of it.

Messers Aquilina, Richard Edwards, and Ian Pople from Bristol was using Omaya reservoir routinely after ETV for every patient;

Routine placement of a ventricular reservoir at endoscopic third ventriculostomy.
Aquilina K. Edwards RJ. Pople IK. Neurosurgery. 53(1):91-6; discussion 96-7, 2003 Jul.

It saved the life of 2 patients in the first three weeks after ETV.

However, I do not recommend the routine use of EVD after ETV for (virgin) obstructive hydrocephalus, not shunted before. It should be indvidualized.

In case of ETV for shunt failure, the condition is a little bit different.

Thank you once again.

Essam Elgamal FRCS(SN)

Question

Thank you Dr. Elgamal for your very interesting presentation.
1. Do you prefer ETV or VPS in patients with systemic infection?

2. Has successful follow-up been obtained with this work?
3. Did you use catheters impregnated with antibiotic in this study?
4. What is your view on ventricular catheter impregnated with antibiotic?

Regards,

Carlos Fernando Lozano-Tangua

Answer

Dear List members,

I would like to thank everyone who have shared this valuable discussion, and addressed questions, I am sure many of us were eager to ask.

Thank you Carlos Fernando Lozano,and I will answer your quetions:

1. Do you prefer ETV or VPS in patients with systemic infection?

In case of acute hydrocephalus in presencre of systemic infection I woud prefer EVD followed by either ETV or VP shunt

2. Has successful follow-up obtained with this work?

Follow up period ranged from 6 months to 2 years and 6 of the 8 patients remained shunt free till present.

3. Did you use catheters impregnated with antibiotic in this study?

We use antibiotic impregnated catheters for VP shunts on regular basis in our unit. For EVD containing a sensor, the one we use and produced by Codman™ is an ordinary catheter with an ICP sensor in it.

4. In your concept and experience, considers a useful option to be the use of ventricular catheter impregnated with antibiotic?

From our experience in the use of antibiotic impregnated ventricular catheter, we notice that the incidence of infection is nearly the same when using ordinary catheters, however, I do recommend antibiotic impregnated catheter whenever available.

Thank you once again.

Essam Elgamal FRCS(SN)

Question

Dear Professor Elgamal
thanks for such a brilliant exposition!

my question is:
would you recommend monitoring of intracranial pressure in all patients after ETV; otherwise which patients are best for monitoring of the ICP

Thanks

Juan Bosco G Torres MD

Answer

Dear Dr.Torres

Thank you for your questions.

I do not recommend the use of EVD and/or ICP for every ETV. I only found it useful in ETV for shunt failure, as I was not sure about the normal CSF drainage and absorptive capacity after a probably long period where the patient was totaly dependent on the shunt for CSF drainage.

Thank you once again

Essam Elgamal FRCS(SN)

Paediatric ependymomas

George Jallo MD

Comment

Dear George,
I hfound the presentation very enlightening and helpful. Thank you for taking the trouble to put it all together.

I would like to make a few observations and seek your advice and opinion on the following areas:

a. Gene Expression and Clinical correlation:

Recent studies point to genetic grouping and extent of surgical resection contribute significantly to outcome whereas histopathology, age, and other clinical parameters did not.

i. In one study 91% of recurrent tumours showed one or more chromosomal imbalances

ii. When comparing CGH results from both primary and recurrent tumours 85% showed additional abnormalities at recurrence with 57% progressing from a balanced profile in the primary to an unbalanced profile in the recurrence.

b. Adverse Effects

Gain of 1q and associated loss of 10p

1. The most frequent imbalance in recurrent tumours was gain of 1q occurring in 72%. In 27% gain of 1q was seen with concurrent loss of 10q.
2. Gain of 1q has been shown to adversely affect survival in neuroblastoma, Wilms' tumours, and Ewing's sarcoma.

c. Favourable Outcome

i. SOX9 expression is associated with a better outcome in paediatric ependymomas

d. Grateful for your feedback on the molecular analysis for classification of tumours, for treatment strategy, prediction of recurrence and ultimately to correlate genetic factors with survival in ependymoma?

2. Evidence that ependymomas from different locations within the central nervous system (CNS) are distinguishable at a genomic level.

a. Several genes are characteristic for tumour location.

i. Intracranial ependymomas are characterized by:

1. the over-expression of EMX2, MSI2, ABCG1, FLT1, TOP2A, CRIM1, CAMK2D, TFPI2, EBI2, ACTR3, NRCAM, PAX3

2. Down-regulation of ADAM9, TFAM, EDN1, and GAS2L1

ii. Supratentorial ependymomas are associated with up-regulation of EMX2, MSI2, ABCG1

iii. Infratentorial ependymomas are characterized by the over-expression of PAX3, NET1, and MSX1

iv. Spinal Ependymomas show over-expression of HOXB5 and HOXA9 83

b. This growing body of evidence for genetic and epigenetic association with different locations of ependymomas suggests the need for targeted treatment. Currently all ependymomas are treated in the same fashion. Are there in your opinion any therapeutic strategies that are or could take advantage of this improved understanding of how ependymomas and genes relate?

3. Potential biological markers of prognosis in paediatric ependymoma

a. Tumours proliferation, reflected by Ki-67 positivity, is an important factor in the discrimination between low- and high grade ependymoma and is a more reliable unfavourable prognostic factor than is histological grading[i]

b. When dealing with parents, how do you report prognosis in your practice and what markers do you find useful?

4. Ependymoma cancer stem cell

a. An important recent finding is that gene expression signatures of ependymomas from different locations of the CNS correlate with those of the corresponding region of the normal developing CNS.

i. The differentially expressed genes are predominantly involved in the regulation of neural precursor cell proliferation and differentiation.

b. Ependymomas contain rare populations of cancer stem cells resembling radial glial cells. In mice, they give rise to tumours.

i. These radial glial cells (in different parts of the CNS) may be transformed into cancer stem cells of supratentorial, infratentorial, and spinal ependymomas.

c. Signalling pathways involved in the development of the brain and neural stem cells, such as Notch, Wnt, SHH, and p53, are important in the pathogenesis of ependymomas.

d. I would be grateful if you could let us know of existing or up-coming strategies based on epigenetic factors and signalling pathways, that are targeting cancer stem cells or tumour in ependymomas.

5. Chemotherapy:

a. As an adjuvant treatment, radiotherapy can be effective, but has the potential to damage the child's developing nervous system at a crucial time-with a resultant reduction in IQ and cognitive impairment, endocrinopathy, and risk of second malignancy.

b. Over half of childhood intracranial ependymomas occur in children younger than 5 years.

c. Because of the above problems, recent studies have focused on the utility of chemotherapy followed by second-look surgery prior to radiotherapy in those patients whose tumours are not totally, or near-totally, resected.[ii]

d. Increasing evidence suggests that ependymomas are chemosensitive, but in older children chemotherapy has been primarily reserved for those patients with subtotally resected tumours or with anaplastic lesions.

e. In very young children, especially those younger than 1 year, treatment with chemotherapy is often used in attempts to delay and, in select cases, obviate the need for radiotherapy, but high-dose chemotherapeutic regimens supported by autologous peripheral stem cell rescue have not been effective.[ii]

f. A significant proportion of children with ependymoma can avoid radiotherapy with prolonged adjuvant chemotherapy.[iii]

i. In a multi-centre study in France, looking at postoperative chemotherapy without irradiation for ependymoma in children under 5 years of age, the overall survival at 4 years was 74% (95% CI, 59% to 86%) for the patients in whom resection was radiologically complete and 35% (95% CI, 18% to 56%) for the patients with incomplete resection.

ii. Deferring irradiation at the time of relapse did not compromise overall survival of the entire patient population.

g. A similar study in the UK using primary chemotherapy post-surgical resection reported that radiotherapy could be avoided or de-

layed in a substantial proportion of children younger than 3 years without compromising survival.[ii]

i. These results suggest, therefore, that primary chemotherapy strategies have an important role in the treatment of very young children with intracranial ependymoma.

h. Grateful for your comments and views on the above points relating to the use of chemotherapy in ependymomas.

6. Radiotherapy:

a. Considering that surgical failures are predominantly local and that there is no apparent benefit from prophylactic irradiation some centres recommend local field irradiation with doses above 50.0 Gy for all children over 3 years with intracranial ependymomas, without meningeal dissemination at diagnosis. [iv]

b. Conformal radiation therapy techniques are primarily used in children with ependymomas, and radiotherapy has now been used in cooperative group studies in children as young as 1 year.

c. Increasing evidence suggests that supratentorial ependymomas differ biologically from those arising in the posterior fossa.

i. Although standard treatment of partially resected supratentorial ependymomas is the same as for partially resected posterior fossa tumours, some studies are evaluating the efficacy of surgery alone for totally resected supratentorial tumours.

d. What is your view on the above points relating to radiotherapy?

Thank you for an excellent presentation on the current best practice and management of ependymomas. I apologize for the number of questions I have posed. Ependymoma is a rare and complex topic and I am grateful for your views.

Kind regards
Guirish Solanki MD FRCS(SN)

i Wolfsberger S, Fischer I, Höftberger R, Birner P, Slavc I, Dieckmann K, Czech T, Budka H, Hainfellner J. : Ki-67 immunolabeling index is an accurate predictor of outcome in patients with intracranial ependymoma. Am J Surg Pathol. 2004 Jul;28(7):914-20.

ii Grundy RG, Wilne SA, Weston CL, et al. Primary postoperative chemotherapy without radiotherapy for intracranial ependymoma in children: the UKCCSG/SIOP prospective study. Lancet Oncol. 2007;8(8):696-705.

iii Grill J, Le Deley MC, Gambarelli D, Raquin MA, Couanet D, Pierre-Kahn A, Habrand JL, Doz F, Frappaz D, Gentet JC, Edan C, Chastagner P, Kalifa C; French Society of Pediatric Oncology. Postoperative chemotherapy without irradiation for ependymoma in children under 5 years of age: a multicenter trial of the French Society of Pediatric Oncology. J Clin Oncol. 2001 Mar 1;19(5):1288-96.

iv Rousseau P, Habrand JL, Sarrazin D, Kalifa C, Terrier-Lacombe MJ, Rekacewicz C, Rey A.: Treatment of intracranial ependymomas of children: review of a 15-year experience. Int J Radiat Oncol Biol Phys. 1994 Jan 15;28(2):381-6.

Answer

I think the future classification for all brain tumors and in particular ependymomas and Medulloblastomas will require the routine molecular analysis of tumor tissue. However at the current time classification and prognosis is still determined by routine histochemistry. I think the future treatment will rely on molecular analysis of these tumors. I do not use any markers to discuss the prognosis with families at this time

The issue for radiotherapy remains controversial as some centers do not advocate any adjuvant therapy for gross total removal of the tumors whereas most still advocate form of radiation therapy,

George Jallo MD

Comment

Dear George,
Thank you for your feedback, this was very helpful. I agree that there is much controversy when it comes to delivering adjuvant therapy in Ependymoma surgery.

I suspect that chemotherapy is not a favorite in your place?

For infants and children <3 years our oncologists use the "Baby Brain" protocol here in order to delay radiotherapy as best as possible.

Kind regards,

Guirish Solanki MD FRCS(SN)

Endoscopic surgery for craniopharyngiomas

C Deopujari MD MCh

Dear Shekhar,
May I congratulate you on a wonderful series of videos expertly highlighting several operative approaches and the sequential use of surgical corridors during tumour resection. I thought the video quality was good and the additional synchronization of image-guidance certainly demonstrated your surgical approach very well.

Frequency of Craniopharyngioma:
Paediatric craniopharyngiomas, although being the commonest non-glial intracranial tumour remain relatively rare. For the whole of England there were only 84 new cases reported in children under the age of 15 years, between 2000 to 2004 (i). There are currently 13 centres performing brain tumour surgery in England. Larger centres may deal with 2-4 new cases per year; other units may see just 1 case per year.

This makes development of expertise more difficult and a case could be made for such surgery to be centralized to two or three centres in the country. Also the surgery that you so expertly demonstrated requires experience and other authors have commented on the experience of the surgeon as a predictor of lower morbidity.

Do you feel that this is a reasonable approach? For a country as large as India is such centralization an achievable or worthwhile goal?

Outcome Prediction in Craniopharyngioma: Radical Surgery vs. Biopsy + Radiotherapy
Predicting risk factors for poor outcome from surgery has been the subject of many studies. I have selected 2 reviews, one performed in 1996 at Great Ormond Street suggesting a flexible approach rather than outright GTR and the most recent large series supporting radical resection as the first and best approach. I am detailing several predictors reported in these studies and how little has changed in them, but how a shift seems to be developing towards more radical surgery.

Predictors in Craniopharyngioma Surgery - 1996(i)i

Predictors of high morbidity included:
- severe hydrocephalus
- intraoperative adverse events
- young age (<=5 years) at presentation

Predictors of increased hypothalamic morbidity included:
- symptoms of hypothalamic disturbance already established at diagnosis
- greater height (>=3.5 cm) of the tumour in the midline
- attempts to remove adherent tumour from the region of the hypothalamus at operation.

Predictors of tumour recurrence:
- large tumour size
- young age
- severe hydrocephalus

Predictors of event-free survival:
- complete tumour resection (as determined by postoperative neuroimaging) and
- radiotherapy given electively after subtotal excision was less likely to be associated with recurrent disease.

Based on these findings, the authors propose an individualized, more flexible treatment approach whereby surgical strategies may be modified to provide long-term tumour control with the lowest morbidity(ii)

Predictors in Craniopharyngioma Surgery - 2010 (iii):

Predictors of Overall survival and progression-free survival
1. GTR in patients with primary tumours at time of presentation

Predictors of increased morbidity & mortality (Factors negatively affecting overall survival and progression-free survival):

1. subtotal resection (recurrent tumours only),
2. tumour size > 5 cm
3. presence of hydrocephalus or a ventriculoperitoneal shunt.

There were no significant differences in the neurological, endocrinological, visual, or functional outcomes between patients with primary and those with recurrent tumours.

Predictors of increased hypothalamic morbidity:
1. Children in the recurrent group have worse hypothalamic dysfunction after surgery than those in the primary group ($p < 0.001$) but no significant difference in BMI ($p = 0.12$).

Predictors of incomplete resection at reoperation:
1. Prior radiation therapy and
2. increasing tumour size.

Tumour Recurrence:
1. In most surgical series, the rate of tumour recurrence has been reported to vary between 0 and 57% (mean 18.3%) following GTR
2. These rates are comparable to the frequency of recurrence or progression following limited resection and irradiation, which varies between 0 and 63% (mean 30%).

In the hands of surgeons with experience with craniopharyngiomas, the authors (iii) believe that radical resection at presentation offers the best chance of disease control and potential cure with acceptable morbidity.

Optimal treatment of paediatric craniopharyngioma:
1. Remains controversial.
2. Survival rates among patients treated with limited resection followed by irradiation are similar to results after radical resection.
3. The risk-benefit analysis of reoperation versus other salvage therapies, however, is unclear. Several authors have reported increased rates of mortality, morbidity, decreased chance of achieving GTR, and decreased OS after reoperation
4. The relative rarity of childhood craniopharyngiomas, the lack of consensus regarding their optimal management, and the potential morbidity of treatment make evaluations of treatment modalities controversial and difficult to interpret.
a. Although some surgeons advocate reoperation for craniopharyngioma recurrence, the utility and safety of this approach are unclear.

Do you consider that the recent interest in radical surgery is related to improved surgical approaches and technique supported by image-guidance and endoscopic surgery as well as the use of combined intracranial and endonasal transsphenoidal approaches?

What do you consider is the reason why you have not seen hypothalamic-related morbidity in your cases?

Do you routinely monitor their endocrine profile and their growth curve?

Given your excellent results, do you now feel that stereotactic biopsy and radiotherapy as first line therapy in children older than 5 years is unreasonable?

Thank you again for an awe-inspiring video and for opening the field to consideration of surgical resection particularly in cystic and in sub-diaphragmatic cases. Grateful for your feedback.

Guirish Solanki MD FRCS(SN)

i. UK Five Year Figures for CNS Tumours (children < 15 y of age, 2000-2004). Data

from National Registry of Childhood Tumours.
ii. Catherine J. De Vile, M.A., M.R.C.P., David B. Grant, M.D., F.R.C.P., Brian E. Kendall, F.R.C.R., Brian G. R. Neville, F.R.C.P., Richard Stanhope, M.D., F.R.C.P., Kate E. Watkins, M.A., M.Sc., and Richard D. Hayward, F.R.C.S. Management of childhood craniopharyngioma: can the morbidity of radical surgery be predicted? JNS, July 1996 Volume 85, Number 1
iii. Robert E. Elliott, M.D.,1Kevin Hsieh, M.D., Tsivia Hochm an, M.Sc., Ilana Belitskaya-Levy, Ph.D., Jessica Wisoff, M.A.,and Jeffrey H. Wisoff, M.D.: Efficacy and safety of radical resection of primary and recurrent craniopharyngiomas in 86 children, J Neurosurg Pediatrics 5:30-48, 2010

Question

Excellent video!

Questions

1. How do you choose the operative approach for craniopharyngiomas, i.e transphenoidal, eyebrow, extended approach. What features of the tumor, presentation make one approach more favorable than the other.

2. What is the endocrine outcome for each of the approaches.

3. Do you recommend transphenoidal approaches in children without an
aerated sinus

George Jallo MD

Answer

Dear George,

Answers to the questions:

Choice of approach: First the decision is made if we are aiming for radical or subtotal excision. This will depend upon morphology of tumor (cystic/ solid/ calcified) and the extent apart from visualization of hypothalamus and pituitary.

If the tumour is predominantly cystic, relatively small and sphenoid sinus is not well developed, supraorbital keyhole approach is chosen. If there is multicompartmental tumour with large calcified areas, pterional or interhemispheric frontal route is chosen

If the sinus is not aerated we will not attempt transsphenoidal approach in children unless the skullbase is eroded. Age is not a major constraint as we have been able to use transnasal endoscopic approach beyond 3 years.

If the sella is enlarged or access can be gained infront or behind the pituitary through a well developed sphenoid sinus, transsphenoidal will be preferred. Extended approach will depend on growth pattern around the skullbase.

We have so far performed 12 transsphenoidal procedures for craniopharyngiomas out of 59 cases (over last 9 years), 8 primary and 4 for recurrences. Radical excision in 5, one has small residue under observation and others were subtotal followed later by transcranial surgery in 1, transsphenoidal resurgery in 1 and others treated with radiation later.

Though I do not have the full endocrine assessment worked out, especially as against other approaches, following observations are made by us:

Neurological recovery is quick with ICU stay of 2-3 days only and hospital stay less than 12 days in these cases. DI has been mild and reversible within 6 weeks in over half of these patients. Hyperphagia and obesity has not been seen.

Thanks

C Deopujari MD MCh

Question

Nice work Dr. Deopujari,

- In children, can we forego endoscopy, stealth or other adjunct tools - or are they more needed/necessary?

- The suprasellar extension seems to warrant more guidance/accessory aids, and does this hold true in your experience?

- How can we minimize post-op endocrine & behavioral/developmental issues in the younger children?

Thanks,

Jogi Pattisapu MD FACS

Answer

Dear Jogi,

1. Endoscopy in children, I think has increasing role in curative as well as palliative surgery for craniopharyngiomas.

2. Image guidance, I think, is useful in following areas.:
*Accessing the tumor by transsphenoidal approach to continuously remind yourself of landmarks, especially at the skullbase and locating the boundaries.
*Also to insert catheter in a cyst

In transcranial as well as transsphenoidal surgery, once the cyst is drained, it may not be very useful to assess suprasellar landmarks.

3. We feel the DI is milder and short lasting after transsphenoidal surgery and also feel that ease of dissection from stalk- hypothalamic area affects the endocrine function and would attempt a less radical excision if this dissection plane is not clear. We have not noted obesity, hyperphagia in children operated by transsphenoidal approach.

C Deopujari MD MCh

s

Early Decompressive craniectomy for HI

Angel J Lacerda MD PhD

Question

Dear Dr Lacerda,

Thank you for your interesting presentation on early and late decompressive craniectomy for severe head injury. Do you use 'cooling' of the core body temperature in the management of raised intracranial pressure?

Thank you

Yours sincerely,
G Narenthiran BSc(MedSci) MB ChB MRCSE

Answer

Dr. Naren, thank you for your question:

The management of intracranial hypertension in severe head injuries is a controvertial theme if we see it from evidence based medical point of view. We only have to review the guidelines published on 1995-2000 and 2007 and we will see that there are no RCT to support any of medical or surgical treatment nevertheless, this does not mean that every thing we are doing is wrong.

We really do not use hypothermia in management of intracranial hypertension in these cases for a number of reasons.

1. Induced hypothermia had been used in the treatment of head injury for many years in the world when we started with our treatment protocol. During that time ten trials involving 771 patients reported hypothermic treatment was associated with a 12% non-significant reduction in the odds of death at the end of treatment or final follow-up and the implications for practice based on meta analysis of hypothermia in severe head injuries reported that there were no convincing evidence from the available studies that hypothermia was beneficial in patients with traumatic brain injury and, given the increase in pulmonary infections and other potential for harm, there was no reason to use it outside controlled research studies.

2. The use of barbiturate coma in our protocol failed to reduce the mortality rate in our patients and according to our conditions in ICU we needed a therapy to obtain early ICP control reducing the patient´s exposure time to intracranial hypertension which we obtained with decompressive craniectomy (DC), a controvertial surgical procedure without strong level of evidence because of no RCT had been designed to value its effect on morbidity and mortality but with a lot of papers reporting good results in small series, case reports, *etc*.

More recently the guidelines which reviewed on prophylactic hypothermia in severe head injuries has reported that scientific literature has failed to consistently support its positive influence on morbidity and mortality. With a level III of evidence pooled data indicate that prophylactic hypothermia is not significantly associated with reduced mortality when compared with normothermic controls however, preliminary findings suggest that a greater decrease in mortality is observed when target temperatures are maintained for more than 48 hours.

In any case we have refused the use of other second tier therapies to reduce intracranial hypertension in severe head injured patients and improve mortality and morbidity and, in clinical practice we have used some of them but in our hospital the introduction of DC in the trauma protocol has had a big impact on outcome.

The aim of inclusion of early DC in our protocol was to reduce the secondary brain secondary after trauma. Although our study included a low number of patients and the design is not a RCT, with this procedure we reduced the mortality in 14.8% compared

with the group of patients with conventional treatment. In our opinion to reduce the mortality under this level we have to work with extra-neurological complications and general management of the patients in ICU.

DC is a rescue surgical procedure and there are some mortality risk factors as severity of primary brain insult with influence over the outcome despite the surgical or medical treatment used to obtain ICP control.

Early DC could appear to some as an aggressive procedure but in our experience is effective in reducing the intracranial hypertension within a short period of time over other second tier therapies, improving CPP, cerebral compliance and other intracranial parameters which influence the outcome.

Your sincerely.

Angel J. Lacerda MD PhD

Question

The Syndrome of the trephined is a possible complication of decompressive craniectomy, how do you manage this difficulty problem?

Luis Rafael Moscote MD

Answer

Dear Dr Moscote thank you for your question.

Well this syndrome was seen in few cases in our series and we have used two ways to treat it:

1. Replacing the bone flap (stored in the anterior abdominal wall) to skull defect the sooner the better, and
2. In patients with severe disability or other complication where the skull flap replacement is delayed, we use cranioplasty fashioned from methyl methacrylate which is also effective in treating the syndrome.

I am very grateful by your interest in our presentation. Best wishes to you in the new year and if you have any other question plese let me know it.

Angel J. Lacerda MD PhD

Primary spine chondrosarcoma

Lozano-Tangua CF,Salazar LRM, Cano FAL, Barrios RB, Olier OM, Alcala-Cerra G

Answer

Dear Dr Ratliff
Thanks for very interesting questions about the Chondrosarcoma Case Report and Literature Review

The surgical tratment that we selected for this patient was block resection of the affected segment including T12-L1-L2 with combined anterior and posterior approach. This is a real challenge for the surgeon because that affected segment includes the insertion of the diaphragm and you needs the active participation of thoracic surgeon.

The reconstructive option that we think adequate for this case is the corporal replacement with cylinder and posterior instrumentation two or three levels up and down of the block resection segment. This procedure requires external immobilization with TLSO corset at least six month after surgery.

According to the literature, chemotherapy have not demonstrated to be efficacious in chondrosarcoma but, radiotherapy can improve the progosis.
Sincerely,

Carlos Fernando Lozano-Tangua. MD

Question

What is the contemplated risk of the indicated surgical procedure (*en bloc* excision and instrumentation). Specifically related to the chances of recovery of the lost neurological function

Thank you

Robert Fink MD FACS PC

Answer

For the approach (combined by anterior and posterior) selected in this case, the surgical risks are not negligible because, of the nearness of big vessels and in addition to the potential compromise of the respiratory musculature.

Particularlythis zone is the origin the Adamkiewicz artery - 50 % origin between T9 and T12. If the surgeon injures this artery on surgery, the risk or irreversible neurological damages is very high

A neurologically uncomplicated operation along with post-operative rehabilitation are indispensable for neurological recovery.

Best regardes

Carlos Fernando Lozano-Tangua MD

Blood blister-like aneurysms

Leonidas M Quintana MD

Question

Question 1:

Dr Leonidas Quintana reported his personal and impressive experience with blood blister-like aneurysms (BBAs). BBAs are very difficult to treat surgically or endovascularly because of the fragility of the aneurysmal walls, as well as the dome and the neck.

Traditional surgical approaches (clipping, wrapping plus clipping, trapping with or without bypass) carry a high risk of intraoperative rupture even with the appropiate clip, and also is inherent to the method the risk of stenosis of the afferent artery.

The rationale of endovascular therapies is to obtain the reconstruction of the arterial wall with preservation of the lumen with, at least, theoriccally low risk of aneurysmal rupture during the procedure. Therefore, endovascular treatment seems to me a very interesting option at present and perhaps the first option of treatment for BBAs.

Starting 2010 decade and with the new 3 D angiographical techniques, my first question is if you consider endovascular treatment as the first option for these cases or do you choose microsurgical approach ?

Question 2:

In our experience working together with Dr Alejandro Ceciliano (our Consultant Endovascular Surgeon), the question that arise when we face BBAs is about the method of endovascular technique to be used for reconstruction of the artery wall. Our team prefer closed strut stent with good results. What do you recommend ?

Alejandra Rabadan MD PhD

Answer

Thank you very much for this question because it involves a future project management.

My presentation ends with what I believe is the vision of treatments to make in the coming years, given the rapid development in the manufacture of new stents, coils and vascular fill materials.

If we think that arterial dissections, both subintimal, as sub-adventitial, the last resulting in BBL aneurysms formation at intracranial level, is clearly a disease of the arterial wall, either with acquired basis, such as severe systemic hypertension, or with a congenital substrate, and structural repercussion with bad collagen matrix at the arterial wall.

So,the main idea is to repair the damage produced by this disease, and the main choice, to my reasoning is this repair should be performed by endovascular means.

And immediately answer the question No 2, ideally, coated stents, if local anatomical conditions permit this procedure, since in some treated cases with fenestrated stents plus coils, may occur recurrences and re-filling of the aneurysmal dome.

Leonidas M Quintana MD

Cervical arthroplasty

B Su MD, John Ratliff MD

Question

What is the role of individual surgeon's skill and experience in generating outcomes?

Is it appropriate for practitioners who may occasionally perform cervical disc replacement (CDR) to inform their patients of goals and risks based upon the data from the most expert and experienced surgeons?

Is there any data on the roles of patient characteristics such as age, gender, smoking status on outcomes?

John D Loeser MD

Answer

Thank you for these thoughtful questions.

The role of investigator experience in contributing to outcomes in any surgical study must be considered.

The choice of patient for intervention and the selection of patients for prospective surgical studies each contribute significant potential sources for bias. The difficulty in doing blinded surgical studies is well documented. These concerns are relevant to studies of cervical arthroplasty.

I would proffer, however, that the results of arthroplasty in the cervical spine are comparable to previously reported series on single level cervical discectomy and fusion, perhaps adding to their face validity.

To my knowledge, patient factors such as tobacco use have not been parsed out from the larger studies of disc arthroplasty. Reported prospective studies have comparable patient populations with regard to smoking status, age, workmen's compensation claim status, and other demographic variables in their arthroplasty and arthrodesis arms. This may indicate these patient factors equally affect surgical outcomes in both fusion and disc replacement populations.

Thanks

John Ratliff MD

Question

I wish to thank Dr Ratliff for his interesting presentation. My questions to him are:

a) How does the currently available literature on cervical arthroplasty affect the authors' practice? Do you give patients a choice of cervical arthroplasty?

b) Do the authors believe that the evolution of cervical arthroplasty is financially motivated?

c) Is the main criticism of the current literature on cervical arthroplasty is that, there is no long term outcome data? What length of follow-up would the authors consider adequate?

Ali Nader-Sepahi FRCS(SN)

Answer

I appreciate these thoughtful questions. I will answer each in turn.

a) I explain the option of cervical arthroplasty to each single level cervical disc patient that is evaluated for surgery. For patients who are not good candidates for arthroplasty, I explain my rationale for recommending a fusion procedure.

b) Hopefully the evolution of surgical techniques in general is based more upon achieving optimal patient outcomes. The financial impact of new devices must always be considered, however.

c) The poor understanding of the natural history of cervical spondylosis has been reviewed in other questions. Many authors have noted the 2 year follow-up data reported in the literature may not illustrate the primary potential benefit of cervical arthroplasy, limiting adjacent segment disease. Longer follow-up of these patients will be required to definitely illustrate whether or not these devices favorably impact the natural history of cervical disc disease.

John Ratliff MD

Question

Comment: A critical but balanced overview of the role of cervical arthroplasty in treatment of Spondylotic Cervical Disease.

Q1: With the design of the prosthetic discs having evolving so rapidly, can we translate one comparative study (eg Bryant V ACDF) into CDRs in general?

Q2: Why do you think there is reduced pain (NDI and neck pain score) in the short term? If anything one might expect an increase in pain due to enhances motion at that segment, particularly in patients with facet arthrosis.

Q3: What is the role on Indomethacin or other NSAIDs in reducing premature arthrodesis?

Q4: The question of `adjacent level disease'(ALD) vs `natural progression of cervical spondylosis' is a valid one. In this context, how can a study prove if involvement of adjacent level is due to ALD rather than natural progression or *vice versa*?

Q5: Is there any indication so far about the long-term complications from CDR, eg: arthrodesis, subsidence, subluxation etc. Any experience on how these complications if any were managed?

Likhith Alakandy FRCS(SN)

Answer

A1.Excellent question. Different disc designs have different device articulations (semi-constrained vs. unconstrained), different compositions (titanium vs. CoCr vs. stainless), and different vertebral body articulations (keel vs. screws vs. flat articulation). While the general tenets of motion preservation via arthroplasty device likely can be translated, the details of the individual devices likely will impact their outcomes and success rates.

A2: Severe facet arthropathy was an exclusion criteria used by the studies, so hopefully the patients did not have severe facet pain. Could the early reduction come from the patients knowing they had been randomized to the study population? Some critics of cervical arthroplasty have noted that the earlier return to function in arthroplasty patients likely can be attributed to eliminating the need for a cervical orthosis, perhaps this plays a role in post-operative pain as well.

A3:eWe routinely used post-operative NSAIDs in our arthroplasty patients for premature arthrodesis. Usually patients are maintained on indomethacin for 2 weeks after surgery.

A4: Fantastic question. What is the natural history of cervical spondylosis? Can we/how can we intervene to favorably affect that natural history? Our lack of knowledge in this respect makes assessment of arthroplasty devices and of the long-term effects of arthrodesis challenging. Only with long-term (10 year plus) follow-up of these patients will answer this question.

A5: There have bee reported cases of arthrodesis at the device site. No intervention for these cases has been reported. Late subsidence may pose a concern, but reports of subsidence in the literature are very limited. Perhaps the large foot-print of present devices decreases the likelihood of subsidence. A

few patients in earlier arthroplasty studies have been involved in motor vehicle collisions, without suffering implant failure, perhaps indicating a low risk of implant traumatic subluxation. A more concerning finding would be late instability/hypermobility at the operated site, with implant subluxation. There, a revision with partial/full corpectomies at the operated levels likely would be required. I have not experienced these complications in my practice.

Thanks again for your thoughtful discussion.

John Ratliff MD

Question

I enjoyed your presentation very much, I am interested in cervical spine surgery since my training with Dr.Caspar in Germany

Over 30 years ago, I am pleased to see your critical points towards what I call " expensive fusion " , I did myself all kinds of implants especially Presige, dicocerve, etc., the long term results are not yet available, my friend Dr Ayman Ramadan in Geneva has 10 years experience and, he is happy with the overall results; he is the inventor of Discocerve and published many studies , but again the work is funded by a company, financial factors and companies influence can not be ignored while studying the literature.

Congratulation for a great presentation.

Hani Meniawi MD

Question

Were there series using, as controls, patient who either had no surgery at all, or who just had anterior or posterior decompression (without instrumentation)?

Can CDR be used (late) in patients who had previously been decompressed (posteriorly) and who had subsequently developed kyphosis?

Can the short follow-up time (2 years or less) in most of these studies justify the use of the CDR approach outside of clinical trials? The long-term benefits (vs. the expense) are unclear.

Robert Fink MD

Answer

Thank you for these interesting queries. To my knowledge, the controls used in the studies from the United States all use single level instrumented ACDF procedures as their control group. I do not believe the studies considered uninstrumented ACDFs, nor any posterior decompressions. I would have to agree with this approach to the study design; consideration of response to posterior foraminotomy is an interesting observation, though.

I believe fixed malalignment, such as the kyphosis noted in your second question, would be a relative contraindication to cervical arthroplasty. If the patient had a fixed kyphotic deformity, it is unlikely that the arthroplasty device would be of benefit. For patients that have failed cervical foraminotomy, it will be interesting to see in future reports if cervical disc arthroplasty will play a role in their treatment. In these patients, the degree of facet arthropathy and maintenance of preoperative cervical motion at the level targeted for arthroplasty may prove to be the limiting factors.

Your last question is particularly insightful. The primary indication for cervical arthroplasty is not poor clinical results with cervical arthrodesis; the clinical outcomes reported in fusion studies with similar follow-up are quite good. The real indication, which has yet to be demonstrated with long-term follow-up studies, is whether or not arthoplasty will limit the need for revision surgery in these patients. Only with longer

term follow-up of the study populations will this question be answered.

John Ratliff MD

Aquaporin-4

Filipiddis A, Tsonidis C

Question

What do the authors believe is the most likely clinical importance of the Aquaporin-4 in brain tumours?

How do the authors intend to further investigate the potential therapeutic modulation of Aquaporin-4 in brain tumour oedema?

Paul L Grundy BM(Hons) MD FRCS(SN)

Answer

Dear Mr. Grundy,

We would like to thank you for your questions about AQP4. We'll try to answer point by point.

Brain tumors especially those that demonstrate an edematous potential and thus a more malignant behavior as a space occupying lesion present mainly with vasogenic edema. Aquaporin-4 in animal models (AQP4 knockouts) demonstrates an up-regulation of its expression and at the same time attenuates vasogenic edema. Possibly these two observations shed light to a protective role of AQP4 in vasogenic edema. It seems that act like "edema scavangers" and aid in elimination of brain water content via the three routes of showed in our presentation. Theoretically a potential theraupetic target of this observation would be the activation or up-regulation of AQP4 in order to aid peritumoral edema clearance.

Another less known property that AQP4 shows is the ability of this protein to aid the migration of astrocytes. The lack of AQP4 in astroglial cell is associated with reduced migration of astrocytes during glial scar formation. This property is observed in migration studies and wound healing protocols but what if this property is a key property of malignant glial tumors in order to spread? This is of course another tricky question underlying the function of AQP4s.

References:

Papadopoulos et al. Aquaporin-4 facilitates reabsorption of excess fluid in vasogenic brain edema. FASEB J (2004) vol. 18 (11) pp. 1291-3

Verkman et al. Three distinct roles of aquaporin-4 in brain function revealed by knockout mice. Biochim Biophys Acta (2006) vol. 1758 (8) pp. 1085-93

Filipiddis A, Tsonidas C

Question

Thank you for the work & presentation on Aquaporins.

- Do you have experience or suggestions for modulators of AQP's, which may be used to improve brain fluid circulation or reabsorption?

- any hopes of regulating these water channels to make them function uni-directionally? I understand that some AQP's are cation-regulated, & may be functionally induced and gated to flow selectively.

Please help us understand these concepts more clearly for potential future clinical benefits.

Jogi Pattisapu MD

Answer

Dear Dr. Pattisapu,

We would like to thank you for your questions.

At present we do not have an experience about AQP modulators. The research in mainly guided to localization of AQPs in dif-

ferent types of tumors and diseases. The suggestions in AQP selective modulation can rely only on a theoretical perspective since to our knowledge, the race for AQP4 specific agonist or antagonists is inconclusive in literature at the present time. Toxic inhibitors exist (sulfadiazine and AgNO3) which are inadequate for clinical research. Most efforts rely on diuretics like acetazolamide or bumetanide derivatives (Tanimura et al, Yool et al). Other efforts rely on antiepileptics which in one paper (Huber et al) showed inhibition of AQP4 in vitro which was not confirmed by other authors (Papadopoulos et al). There is also a report of thrombin inhibiting AQP4. There are few of published papers that state that AQP is modulated but more evidence needs to be presented since there are a lot of steps between a potent AQP4 modulator and drug development.

Huber et al. Inhibition of aquaporin 4 by antiepileptic drugs. Bioorg Med Chem (2009) vol. 17 (1) pp. 418-24

Niemietz and Tyerman. New potent inhibitors of aquaporins: silver and gold compounds inhibit aquaporins of plant and human origin. FEBS Lett (2002) vol. 531 (3) pp. 443-7

Papadopoulos and Verkman. Potential utility of aquaporin modulators for therapy of brain disorders. Prog Brain Res (2008) vol. 170 pp. 589-601

Tang et al. Thrombin inhibits aquaporin 4 expression through protein kinase C-dependent pathway in cultured astrocytes. J Mol Neurosci (2007) vol. 31 (1) pp. 83-93

Tanimura et al. Acetazolamide reversibly inhibits water conduction by aquaporin-4. J Struct Biol (2009) vol. 166 (1) pp. 16-21

Yool et al. Roles for novel pharmacological blockers of aquaporins in the treatment of brain oedema and cancer. Clin Exp Pharmacol Physiol (2009) pp.

Well this is a pretty good point and perspective that relies on electrophysiology (Yool et al). It is true that in astrocyte foot processes AQP4 co-localises with a specific K+ ion channel named Kir4.1. This channel contributes mainly to setting membrane potentials and stabilizing basal state of a neuron. These channels give the endfoot processes of the glia, at the point they surround the blood vessels, the property to sink excess K+ and water. So you are right when you argue about a form of cation-"regulation" of AQP4 meaning that AQP4 in glial cells get water out at the point of Kir4.1 co-localization which is the endfoot processes of astrocytes but the protein that is the key player in AQP4 polarization in α-syntrophin. The modulation of this behavior is tricky if it is attempted via electrophysiology and ion channel modulation only cause there are a lot of different ion channels in astrocytes with a difficult to predict electrochemical behavior locally. Only models can attempt to predict in an electrochemical change at this territory.

Yool. Aquaporins: multiple roles in the central nervous system. The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry (2007) vol. 13 (5) pp. 470-85

Aristotelis Filippidis and Christos Tsonidis

Question

Question 1

AQP-4 is an attractive target for drug discovery. It is expressed in astroglia, most strongly at the blood-brain and brain-cerebrospinal fluid barriers. (Papadopoulos MC et al. Prog Brain Res 170: 589-601, 2008).

Recently, Moeller HB et al reported an *in-vitro* expression study that demonstrated at the molecular level a functional link between vasopressin receptor V1(a) R and AQP-4. They concluded that this molecular interaction may prove to be a potential therapeutic target in the prevention and treat-

ment of brain edema. (Neuroscience (2009) 164(4): 1674-84).

Dr Filippidis et al, I would like to ask you: Considering that the vasopressin V1(a) R has a negative modulating effect on AQP-4, what do you think about the potential therapeutic role of the Relcovaptan, a non-peptide inhibitor of the antidiuretic hormone (vasopressin) receptor, selective for the V1a subtype or other AQP-4 modulators that could offer new therapeutic options for brain edema?

Question 2

A down-regulation of AQP-4 in the different structural lesions of the brain demonstrated a reduction of brain edema formation as it was reported by several authors:

- "NG WH et al. J Clin Neurosci 16 (3): 441-3, 2009
- "Fazzina G et al . J Neurotrauma 2009
- "Hirt L et al. J Cereb Blood Flow Metabol 29 (2) : 423-33, 2009
- "Moeller HB et al .Neuroscience164 (4): 1674-84, 2009
- "Tait MJ et al. Trends Neurosci 31 (1) : 37-43, 2008
- "Papadopoulos MC et al . Prog Brain Res 170: 589-601, 2008
- "Küppers E et al. Eur J Neurosci 28 (11) : 2173-82, 2008
- "Fu X et al. Glia 55 (9) : 2007
- "Yool AJ et al . Neuroscientist 13 (5): 470-85, 2007
- "Papadopoulos MC et al. Pediatr Nephrol 22 (6) : 778-84, 2007
- "Sawada T et al. Brain Tumor Pathol 24 (2) : 81-4, 2007

However, we couldn't find any report on a very interesting model of pure brain edema as is the benign intracranial hypertension syndrome, also called pseudo tumor cerebri. What do you think about this disease and the possible role of AQP-4?

Alejandra T Rabadán MD, PhD

Acknowledgment:
I would like to thank Dr Pablo Azurmendi from the Kidney Laboratory of the Institute of Medical Research A Lanari, University of Buenos Aires (UBA)- CONICET, for their generous contributions to the discussion of the paper. Email: pabloazur@hotmail.com

Answer

Dear Professor Rabadan,

We would like to thank you and Dr. Azurmendi for your thorough review of our presentation and your insightful questions derived from the literature and created this discussion.

The most critical point in an effort to propose an adequate possible role of aquaporins and especially AQP4 is the understanding of different effects of these proteins and thus their potential modulators in different types of brain edema based on Klatzo classification[7]. It is well established in *ìn vivo* animal models that cytotoxic brain edema which is mainly the cornerstone of hypoxia, ischemia or meningitis induced edema is reduced when AQP4 is not present (in AQP4 mice knockouts) while vasogenic edema observed in peritumoral edema and brain abscesses is related to AQP4 up-regulation which finally reduces vasogenic brain edema. The whole picture of pathophysiology is further perplexed since AQP4 are two-way water transport channels[13,14].

The first question that has to be answered is what type of brain edema do we intend to treat by AQP4 modulation since various responses exist, related to whether the edema is mainly vasogenic or cytotoxic. Let's choose the option of brain tumor edema which is described in our presentation and it is a classic model of vasogenic edema. Then we should decide about the desired effect. Although the AQP4 expression is up-regulated in brain tumors it seems that this observation is related to the effort of the organism

to eliminate excess water in brain produced by blood-brain-barrier disruption via an AQP4 dependent pathway[13]. Thus the desired pharmacological agent, should activate or up-regulate AQP4 in cases that the resolution of vasogenic edema like brain tumor edema is the target *in vivo*. In other words AQP4 in vasogenic edema gets water out of the cerebral matter.

The results of the study of Moeller et al[9], present an *in vitro* negative modulating effect between AQP4 and activation of V1a Receptor via vasopressin. This activation decreases water permeability and leads to internalization of AQP-4 in membrane. It is risky to extrapolate *in vitro* results *in vivo* reality. We should also remember that these results are demonstrated in Xenopus laevis eggs and not brain matter, not even astrocytes. In theory, a selective V1aR blocker like Relcovaptan could show opposite results in this setting and increase water permeability in a route out of the membrane, thus getting water out of the cell. If you want to resolve vasogenic edema you have to drive the water out of extracellular space, to elimination routes demonstrated in our presentation. In order to see if this effect leads to resolution of vasogenic edema *in vivo*, animal models are needed. Of course the drug should possess the ability to pass BBB and concentrate in active concentrations in brain but this is not a problem in vasogenic edema where there is BBB disruption. Opposite results could be observed in other types of brain edema so a correct and representive choice of an animal model with brain edema is a prerequisite. These principles of course should used for every AQP4 candidate modulator.

ANSWER to QUESTION 2:

It is observed that a down-regulation or loss of AQP4 in knockouts does not reduce brain edema universally in all cases. As it was stated in *ANSWER to QUESTION 1*, different types of brain edema respond differently in up-regulation or down-regulation of AQP4[13,14].

There is a lasting controversy in the literature concerning the presence of cerebral edema in patients with idiopathic intracranial hypertension (IIH or pseudotumor cerebri)[4]. Early theories and reports in 80s and 90s, supported the presence of cerebral edema in benign intracranial hypertension syndrome[5,10,16,17]. Most of these studies were MRI diffusion studies involving a total of 39 patients with IIH. More recent evidence derived from clinical, neuroimaging and histopathological data support the thesis that there is no evidence of significant cerebral edema in pseudotumor cerebri[3,4,20]. Patients with IIH do not present with coma or altered level of consciousness, which is the clinical picture of patients with cerebral edema. Measurements obtained with an MRI T1W water diffusion weighted protocol in 10 patients with IIH and 10 weighted control patients failed to demonstrate trans-ependymal water flow leading to diffuse cerebral edema[3]. Also, autopsy data from IIH patients did not reveal the presence of cerebral edema[20].

It seems that literature is inconclusive about cerebral edema presence in IIH and more studies of larger size are needed. Cerebral edema presence in IIH is a question to be answered if we want to define a possible role of AQP4. In case that cerebral edema does not exist in this setting we do not think that AQP4 could possibly demonstrate a role in the pathophysiology of the disease since the presence of cerebral edema is a prerequisite for an augmented functional role of AQP4. In case that cerebral edema exists as earlier studies indicate, this type of edema shows increased transependymal flow and thus it is categorized to hydrocephalic edema according to Klatzo[7,16]. Your observations about the lack of studies concerning AQP4 and pseudotumor cerebri are true and intriguing about the start of a novel protocol. Only implications can be made for IIH and the behavior of AQP4 in patients with increased

transependymal flow since most animal models studying hydrocephalus and aquaporins rely on kaolin induced hydrocephalus which is a form of non-communicating hydrocephalus model[19] while in IIH, hydrocephalus is not present and intracranial hypertension is attributed mainly to a communicating CSF absorption defect due to dural venous hypertension[4,6,11,12,15]. The most closely related model found till now (a model with communicating CSF obstruction and increased transependymal flow) is the paper of Tourdias et al[18]. In this study a communicating, inflammatory hydrocephalus model based on rats is used for identifying AQP4 expression in this setting. The authors found that AQP4 is up-regulated and probably a protective mechanism. Idiopathic intracranial hypertension is more common to obese females (and it can even be reversed after weight reduction measures) is related to increased dural venous pressure, reduced CSF absorption and possibly neuroendocrinological alterations like leptin production[2,4,6,11,12,15]. It seems that treatment directed to venous pressure reduction could possible be the clue to adequate etiological treatment while symptomatic treatment can be accomplished with shunting and or repeated lumbar punctures.[4]

In cases that the theory of increased CSF production from choroid plexus is proposed as an alternative to the venous hypertension[4], the role of AQP1, which is related to CSF production[1,8] might be significant.

We wouldT like to thank you for the opportunity to have this discussion,

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Aristotelis Filippidis and Christos Tsonidis

Unruptured intracranial aneurysms

Robert E Harbaugh MD FACS

Question

Dear Dr Harbaugh,

Initially I wish to express how honored I feel to participate with you in this important meeting and I wish to congratulate the organizers for this marvelous idea.

Dear Professor Harbaugh, we consider your presentation very important. For many years we have read from several papers about microsurgical treatment and more recently endovascular coiling for unruptured intracranial aneurysms (Robert Solomon and others authors).

We know that there is enough evidence to arrive at an ideal treatment option for each such patient.

However, some patients of our institution had rejected the offered surgical treatment for unruptured intracranial aneurysms yet, they remain healthy at more than 5 years of follow-up.

We are agree with you it is necessary to obtain a strong evidence for the best treatment and ponder if the conservative treatment could be an option for some patients without risk factors of rupture although, we have been treating all patients with UIA.

In your experience and with the current level of evidence do you consider that it is possible that some of this patients with unruptured intracranial aneurysms could stay for a long time under observation?.

Sincerely yours.

Angel J Lacerda MD PhD

Answer

Dear Dr. Lacerda.

Thank you for the excellent question. I elect to follow many patients with incidentally diagnosed unruptured intracranial aneurysms. The decision as to whether to recommend treatment or conservative management is based on a large number of patient and aneurysm specific variables. Patient variables include patient age, medical co-morbidities, history of previous aneurysm rupture, tobacco use, family history of aneurysm rupture etc. Aneurysm specific variables include aneurysm size (absolute and in relation to the vessel of origin), configuration and location. Untreated patients return at six months for follow-up imaging (MRA or CTA). If there has been no change in the aneurysm size or shape at six months the patient is imaged at yearly intervals. We are presently in the midst of a prospective, multicenter study looking at what aneurysm features may predict aneurysm presentation as a ruptured or unruptured aneurysm and, for the unruptured aneurysms, what features predict subsequent aneurysm enlargement and rupture. I am also preparing a larger multi-center study to look at patient and aneurysm features that various cerebrovascular specialists use to determine their recommendations for observation or treatment.

Robert E Harbaugh MD FACS FAHA

Question

Dear Dr Harbaugh,

Thank you for your two excellent presentations related to unruptured intracranial aneurysms!

The prospective ISUIA study is probably the best that we have on the risk of rupture of unruptured aneurysms. However, can the findings of the study be used to assess the risk of

rupture of an unruptured aneurysms for patients India, Middle east or Africa?

Thank you very much for your kind attention and for any of your reply.

Yours sincerely,
G Narenthiran MB ChB BSc(MedSci) MRCSE

Answer

Naren,

Thank you for the kind words. I agree that the ISUIA prospective study is the best we have but the ISUIA results almost certainly underestimate the risk of aneurysm rupture. If a patient in the ISUIA study was evaluated by a vascular specialist and treatment was recommended that patient went on to be treated. Therefore, only those patients who were deemed to be at a low risk of rupture were followed. It is inappropriate to conclude that those patients who were treated would have had the same low risk of rupture if they, too, had been followed rather than treated. We don't know if this group would have had the same rupture risk or not and no *post hoc* analysis will allow to obtain this information. The most parsimonious interpretation of the ISUIA data is that vascular specialists are very good at picking out those aneurysms that would go on to rupture and treating them before they do so. In short, there are many patient and aneurysm specific variables in addition to maximum dimension and location that almost certainly have a profound effect on risk of rupture. Vascular specialists take these into account when making treatment recommendations.

In regard to smoking and aneurysm rupture, I cannot prove that patients with an unruptured aneurysm who smoke are at increasd risk of rupture. However the data are very clear that smokers are strongly over-represented in aneurysmal SAH patients compared to the general population. This being the case it is reasonable to assume that patients who smoke are at increased risk of forming intracranial aneurysms and that patients with intracranial aneurysms who smoke are at increased risk of rupture.

Robert E Harbaugh MD FACS FAHA

Question

Dear Prof Harbaugh,

I would like to congratulate you and your team for this astonishing work! I am sure that a lot of modeling and computational fluid dynamics (CFD) analysis is behind theses slides. This approach is really unprecedented in the area of vascular pathophysiology in CNS and it shows what a collaboration of scientists from different perspectives can achieve. Great work!

Question 1:

Studies from Arutiunov *et al*. identifying the relation of arachnoid trabeculae termed "chordae" and subarachnoid vessels showed that vasospasm and even aneurysm rupture could be related to the microanatomy and physiology of the subarachnoid space apart from the properties of the aneurysm itself. In an era of high Tesla MRIs with great resolution of the subarachoid space, do you believe that apart from the CFD analysis of an analysis of the subarachnoid microenviroment could reveal us different reasons about why some aneurysm rupture and some not ?

Question 2 or a possible perspective:

I would like to ask you some details about the "Isolating the Aneurysm" phase (slides 11 and 12). Why do you choose this cutoff point (slide 11-red line) for final aneurysm mesh analysis? In a 2-D world the definition of aneurysm sac could be fulfilled by choosing a line that crosses the neck of the aneurysm and divides the normal vasculature from the aneurysm sac. In a 3-D reconstruc-

tion world the endpoints of what is an aneurysm or not could not possibly be defined only by a single cutoff point at the sac. If we could carefully see slide 11 bellow the red cut-off line you could see shades of gray that represent various aneurysmatic dilations surrounding the normal pathway of the vasculature which are not included in analysis. You could possibly find interesting stuff including these areas in your analysis since are high pressure areas. Of course these areas are the areas that the aneurysm starts its creation and it could be interesting to see an analysis there. In the 3-D world you could incorporate a cutoff 3-D shape that also includes these areas. Then the 3-D definition of an aneurysm would not be "whatever is above the upper normal vessel wall limit" but "whatever 3D area it bulges away from the normal vessel lumen". I really do not know what the affect of the result could be, but only your team can do this and teach us.

Best regards,

Aristotelis Filippidis MD

Answer

Dear Dr. Filippidis,

Thank you for the kind words.

1. I have long been intrigued by the relation of the subarachnoid space, the lack of an adventitia in brain vessels and the effects of a subarachnoid clot on this system in the pathogenesis of vasospasm. I am less convinced that the microanatomy of the subarachnoid space has any meaningful effect on aneurysm formation and rupture. However, our analysis has not looked at this possibility and at present we do not have any plans to add this to the list of possible factors affecting aneurysm formation, growth and rupture. Even in the era of improved imaging I think this microanatomy would be very difficult to identify. It should be noted that for hemodynamic modeling the effects of G-forces on the aneurysm can be neglected both because of their small magnitude compared to other forces and because G forces affect the blood in the aneurysm and the CSF outside the aneurysm simultaneously and to exactly the same degree thus have a net effect of zero on transmural pressure.

2. You raise a point that has given us a good deal of trouble - how to identify where the aneurysm starts for the purpose of determining the aneurysm surface area, volume, irrgularity and other geometric analyses. Your point that we are using a two dimensional cut point in a three dimensional reconstruction is a good one. We did evaluate the effect of moving the cut plane a small distance in various directions and it did not affect our analysis. It should also be noted that the cut point only affects the aneurysm size and shape calculations and not the fluid dynamics analysis as the entire vascular tree, including the aneurysm, is used for the hemodynamic modeling.

Robert E. Harbaugh MD FACS FAHA

Question

Dear Dr Harbaugh,

On the presentation: Unruptured Intracranial Aneurysms: Who and How to Treat

The natural history of UIAs and treatment outcomes are usually influenced by:
(1) patient factors, such as previous aneurysmal SAH, age, and coexisting medical conditions.
(2) aneurysm characteristics, such as size, location, and morphology strongly related with local hemodynamic factors.
(3) factors in management, such as the experience of the surgical team and the treating hospital.

I should like to have some comment, from Prof. Harbaugh, related with this last point. The experience of the surgical team.

We have to keep in mind, that related with ruptured intracranial aneurysms, in the most extended study, the ISAT, unfortunatelly the patients that entered to the study, were enrolled in centers that didn´t have so much surgical expertise, and the centers had a strong expertise in endovascular treatments. Of course, at the time of performing a statistical analysis, this factors in management are very important in the results.

On the presentation: Predicting Aneurysm Rupture: Computer Modeling of Geometry and Hemodynamics

This wonderful presentation, and project use anatomically realistic 3D geometry and hemodynamic simulation.

In the part 2 of the presentation, related with hemodynamics factors, in the summary of this interesting work, is pointed that pressure is the dominant load on aneurysm: shear stress is no more than 1% of pressure load, and the máximum shear stress value can be larger than that regarded to cause endothelial damage.

I should like to have some comment from Prof. Harabaugh, according with his experience, related with the concept of wall shear stress, because there are some papers demonstrating that a high shear stress state seems to be more of a risk factor and more likely to lead to rupture than a low shear stress state in side wall with branching vessel aneurysms and end wall aneurysms[1] and, in other papers the results indicate that aneurysm growth is likely to occur in regions where the endothelial layer lining the vessel wall is exposed to abnormally low wall shear stress[2].

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Leonidas M Quintana MD

Answer

Dear Dr Quintana

Thanks to Dr. Qintana for his careful review of the presentations and pertinent questions. I fully agree that many factors are involved in the natural history and treatment outcomes for patients with unruptured intracranial aneurysms.

Identifying prognostic indicators of cerebral aneurysm rupture risk has been an area of considerable interest for many years. The size of the lesion is widely considered as one possible determinant of rupture risk. Aneurysm size is easily measured from routine angiograms and would seem to be a logical choice given that larger aneurysms are more likely to rupture. However, data from large population studies, like the International Study of Unruptured Intracranial Aneurysms (ISUIA)[5] suggest that size alone is not a reliable index of rupture risk. Many other factors are routinely considered by cerebrovascular specialists when making a recommendation for treatment for patients with unruptured intracranial aneurysms.[4] For instance, other aspects of aneurysm geometry, including aneurysm shape, may play a role in estimating the risk of aneurysm rupture.[3] Diagnostic imaging reveals that shape can vary significantly between aneurysms of similar sizes. However, there has been little research to rigorously assess aneurysm shape as a prognostic indicator of rupture

risk. Until recently, studies on lesion shape have been confined to using two-dimensional angiographic studies that do not adequately reveal the complex three-dimensional (3-D) nature of intracranial aneurysms. Digital data from computed tomography angiography (CTA), digital subtraction angiography (DSA) or magnetic resonance angiography (MRA) on the other hand allow for a complete characterization of 3D lesion geometry[3]. Patient specific factors such as patient age, a previous history of aneurysm rupture, aneurysm location, a family history of aneurysmal subarachnoid hemorrhage, cigarette smoking, alcohol consumption and hypertension may also affect the risk of aneurysm rupture and the recommendations for aneurysm treatment[4].

Our group was the first to report a methodology to rigorously quantify 3-D aneurysm size and shape. Employing data from CTA of aneurysm patients, we developed and reported a methodology to quantify the 3-D geometry of these lesions using techniques in differential and computational geometry[1]. Subsequently, we performed a preliminary investigation of ruptured and unruptured intracranial aneurysms. We found that certain 3D shape features statistically distinguished ruptured lesions from unruptured ones while all size indices failed to do so[3]. From a biomechanical standpoint, the hemodynamics inside the aneurysm sac and the mechanical tension on the sac wall will be affected by both the lesion size and shape. Recently, computational fluid dynamics investigations and inverse elastostatics finite element analyses of intracranial aneurysms by our group suggest that shape is a determinant of wall shear stress and pressure-induced wall tension[2].

A better understanding of the factors associated with aneurysm rupture and how cerebrovascular specialists use these factors in recommending treatment for patients with unruptured intracranial aneurysms is needed. Such understanding is essential before a meaningful prospective randomized treatment trial of unruptured intracranial aneurysms is designed. If cerebrovascular specialists, who recommend treatment for patients with unruptured intracranial aneurysms, do not believe that equipoise exists among the various management options for most patients with unruptured intracranial aneurysms, they will randomize only a small percentage of patients and these patients may not be representative of the larger patient population. The results of such a randomized trial could have serious adverse effects on determining the best management options for patients with unruptured intracranial aneurysms.

The question raised in regard to the skill of the surgeon and the experience of the surgical team on patient outcomes is a very important one. One shortcoming of prospective randomized trials in surgery is that outcomes are profoundly affected by the skill of the surgeons involved in the trial. If the operating surgeon's skill differs from the skills of the trial surgeons the outcomes will differ as well. Because so many variables, including the skill of the surgical and endovascular practitioners, determine patient outcomes it is impossible to recommend a universal treatment strategy that is appropriate for patients with unruptured intracranial aneurysms. The best we can do is to recommend that patients be evaluated, whenever possible, at institutions who offer both endovascular and surgical expertise in the treatment of aneurysms and rely on the skill and judgement of the clinicians.

In response to the questions regarding shear stress and the risk of rupture it is impossible at present to determine if aneurysm growth occurs because areas of low shear stress cause endothelial thinning in this area or geometric changes result in alterations of shear stress. Because the magnitude of shear stress is so low compared to other forces acting on the aneurysm wall I doubt that high shear stress *per se* poses a significant rupture risk. Based on the distribution of shear stress in aneurysms of varying geometry it seems

plausible that areas of high shear stress may lead to atherosclerotic changes at those locations.2

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