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**Review Article**

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# How Intraspinal Tumors Cause Hydrocephalus: A Systematic Review in the Light of Novel CSF Circulation Model

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## Abstract

This review aims to assess and sum up the proposed pathomechanisms underlying the Coexistence of Hydrocephalus (HC) with spinal cord tumors. The PubMed database search identified 119 publications, of which 23 were eligible for this study. Hydrocephalus was mostly described in the presence of spinal ependymomas and astrocytomas. Tumor cells can compromise the CSF flow (obstructing ventricular outlets and Subarachnoid Space (SAS) of cerebral convexity – impairing function of arachnoid granulations and villi, Virchow-Robin spaces, perineural lymphatics). The leptomeningeal spread may cause communicating HC by detaching thecal sac from cranial SAS, which serves as a CSF reservoir (according to hydrodynamic theory and water hammer effect). Spinal SAS also absorbs some portion of CSF (around spinal nerve roots). The postoperative adhesions in the fourth ventricle (after cervical tumors resection) contribute to HC formation. Hydrocephalus is caused by mere elevated CSF osmolality, specific substances like fibrinogen (which is formed as a result of inflammation or leaks through a compromised blood-brain barrier), and eventually particular proteins like TGF- $\beta$ , EGF, aFGF and PDGF. The classical model of CSF circulation does not reflect reality - CSF is indeed mostly produced by choroid plexus, however robustly supported (~30%) by production in the endothelium of Virchow-Robin spaces capillaries and ventricular ependyma. It can be absorbed all over ventricular lining, outside ventricles into Virchow-Robin Spaces, cervical lymphatics and spinal nerve roots. Breathing, opposed to vessels pulsation appears to be the main force for CSF movement. The increased venous pressure, common in malignancies, also impairs CSF absorption.

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## Introduction

The occurrence of communicating hydrocephalus among patients with spinal cord tumors is a relatively rare - affecting approximately 1% of them - but still not fully explained phenomenon [1]. Malignant tumors are more likely to be linked with Hydrocephalus (HC) [2]. There are many reports of such a condition and few hypotheses have been proposed [1,3,4-14]. However, an up-to-date summary of all possible pathomechanisms that might underlie such conditions as spinal cord tumors causing communicating hydrocephalus in both pediatric and adult population is lacking [13-15]. Furthermore, no analysis has been carried out of the foregoing phenomenon reflecting on a new model of Cerebrospinal Fluid (CSF) circulation - each is founded on a classical model [1,3,5-14,16-24].

The aim of this article is to review available scientific articles describing the occurrence of communicating hydrocephalus in the presence of spinal cord tumors in order to sum up all proposed hypotheses of its pathomechanism and scrutinize them in the light of recent findings on the dynamics of fluid circulation. Summing what is already known about this condition highlights what exactly should be investigated in upcoming research to confirm or disprove existing hypotheses.

## Methods

### We used the PubMed database via the following search terms

“Best matches for:” “spinal intradural tumor AND hydrocephalus OR spinal subdural tumor AND hydrocephalus OR spinal intradural tumor AND ventriculomegaly OR spinal subdural tumor AND ventriculomegaly OR intramedullary tumor AND ventriculomegaly OR intramedullary tumor AND hydrocephalus”.

This revealed 119 publications, which were consecutively analyzed to find all the cases of intraspinal tumors with coexistent but not preexisting hydrocephalus or pseudotumor cerebri.

The exclusion criteria constructed to avoid cases where the cause of HC was clear and well understood were as follows:

- End-stage of the neoplastic disease with massive intracranial seeding
- Extensive bleeding (solely post-subarachnoid hemorrhage (SAH) hydrocephalus)
- Other clear cause for hydrocephalus (e.g. other mass in the cranium)
- Full article not available (or in other language than Polish/English)

This analysis eventually emerged 23 scientific articles [1,3,5-14,16-26]. The level of evidence of these articles was assessed according to the criteria in (Table 1), adapted from [30].

As there were no instances of tumors causing CSF overproduction in included papers, an additional search was performed. Again, the Pubmed Database was searched with following terms: “csf overproduction AND spinal tumor OR cerebrospinal fluid overproduction AND spinal tumor OR csf overproduction AND spinal neoplasm OR cerebrospinal fluid overproduction AND spinal neoplasm”, and no articles were found. Another, more liberal search: “CSF overproduction AND tumor OR CSF overproduction AND neoplasm” showed 41 articles, of which none described a single case of intraspinal tumor (IST) causing CSF overproduction – most of the papers described choroid plexus papillomas, where the CSF overproduction is well documented and understood presently [19,27-31].

## Results

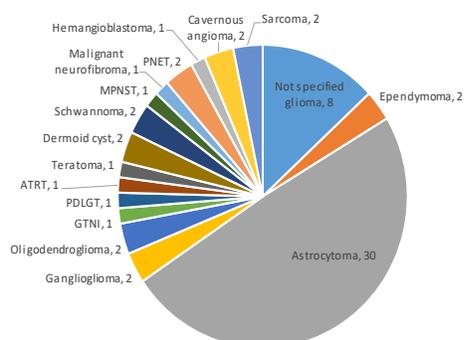
The oldest of the included publications dates back to 1981, and the most recent one to 2018. Quantifiable information from included studies has been consolidated and structured into (Table 2 and Figure 1).

**Table 1:** Type of evidence classification [26].

Level of evidence	Type of evidence	Number of included papers with corresponding evidence level
1	Randomized controlled trials; meta-analysis of randomized controlled trials	0
2	Prospective, comparative trials; heterogenous meta-analysis	2
3	Retrospective reviews; case-control studies	9
4	Case series	1
5	Case reports; expert opinion; personal observation	11

**Table 2:** Summary of quantifiable information from included studies and histological types of described tumors.

	Level of evidence	Study population	No. of patients with HC	Spinal level			Depth		Histological type	Bleeding tumors
				C	Th	L/s	IDE	IDI		
<i>Wu et al. 2018</i>	3	8	3	0	7	1	X	X	atypical teratoid rhabdoid	3
<i>Khoulali et al. 2018</i>	5	2	2	0	0	2	0	2	schwannoma ependymoma	X
<i>Hale, Fricker, and Crook 2018</i>	5	1	X	X	X	X	X	X	X	X
<i>Kushel', Belova, and Tekoev 2017</i>	2	541	32	X	X	X	0	32	X	X
<i>Rangwala et al. 2017</i>	5	1	1	1	1	1	0	1	pilocytic astrocytoma WHO grade I	X
<i>Borkar, Mahapatra, and Bansal 2014</i>	5	1	1	1	1	0	0	1	pilocytic astrocytoma WHO grade I	X
<i>Morais et al. 2017</i>	5	1	1	0	1	0	0	1	hemangioblastoma	X
<i>Sublett et al. 2017</i>	5	1	2	X	X	X	1	0	PNET	X
<i>Katoh et al. 2014</i>	5	1	1	0	0	1	1	0	cavernous angioma	1
<i>Serra et al. 2013</i>	5	1	1	0	1	1	0	1	glioneuronal tumor with neuropil-like islands (GTNI)	0
<i>Serra et al. 2013</i>	5	1	1	1	1	1	0	1	PNET	X
<i>Mirone et al. 2011</i>	3	X	X	X	X	X	X	X	X	X
<i>Galarza et al. 2006</i>	3	2	2	1	1	0	0	1	astrocytoma	X
<i>Porter et al. 2006</i>	5	1	1	1	1	0	0	1	astrocytoma	X
<i>Iannelli, Lupi, and Castagna 2007</i>	5	1	1	0	1	0	0	1	capillary hemangioma	0
<i>Vassilyadi and Michaud 2005</i>	5	1	1	1	1	0	0	1	Astrocytoma WHO grade III	0
<i>Cinalli et al. 2009</i>	2	8	8	X	X		0	8	gliomas	X
<i>Makino et al. 1995</i>	5	1	1	0	0	1	0	1	cavernous hemangioma	1
<i>Prasad et al. 1994</i>	5	1	1	1	0	0	0	1	astrocytoma	1
<i>S Rifkinson-Mann, J H Wisoff n.d.</i>	3	25	25	31	39	19	X	X	2 gangliogliomas 20 astrocytomas 2 mixed oligodendro-astrocytomas 1 ependymoma	X
<i>Heye et al. 1990</i>	5	X	X	X	X	X	X	X	X	X
<i>Feldmann et al. 1986</i>	3	1	1	0	0	1	1	0	benign schwannoma	0
<i>Oi and Raimondi 1981</i>	3	64	9	X	X	X	4	3	Astrocytoma mixed glioma 2 dermoid cysts Teratoma malignant neurofibroma 2 sarcomas (mets)	0
<b>TOTAL</b>	<b>N/A</b>	<b>664</b>	<b>95</b>	<b>38</b>	<b>55</b>	<b>28</b>	<b>7</b>	<b>56</b>	<b>61 described histological types</b>	<b>6</b>



**Figure 1:** Types of tumors coexisting with HC.

We have arranged the proposed pathomechanisms into groups and further into subgroups, based on organic or physical agents causing this flow impairment. According to this classification, they have been consolidated in (Tables 4,5 and 6) and will herein after be discussed.

#### Tumor cells compromising CSF flow

Dissemination of the tumor as a cause of HC was proposed by 8 authors [5,6,8,17,20] (hypothesis present in 36% of all papers) and quoted by 11 [1,3,5,7,10,19] (in 50 % of all papers). Among spinal tumors, ependymomas and astrocytomas are the ones most often causing hydrocephalus [32]. These two histological types are

also the two most common ones among intradural intramedullary (IDI) tumors - 60% to 70% being ependymomas and 30% to 40% astrocytomas [33]. Kushel et al. have analyzed a population of 541 surgically treated patients with IDI tumors. They observed the general prevalence of HC among patients with IDI tumors in 5,6% of patients with benign (WHO Grade 1-2) IDI tumors, and in 8,3% of patients with malignant tumors (WHO Grade 3-4) [24]. The crucial metastases implantation locations include proximity of ventricular outlets: Monro, Magendie and Luschka foramina – leading to development of oHC. Compromising the Subarachnoid Space (SAS) of cerebral convexity effects in development of cHC by impairing Arachnoid Granulations (AGs), and potentially another, recently proposed absorption sites like Virchow – Robin (V-R) spaces [34]. As an implication of SAH, meningitis, the inflammatory process causes scarring and obstruction of AG dysregulating CSF homeostasis and causing HC, proving the weight of properly functioning AGs, however reported as minor [35]. The spread and implantation into leptomeninges was referred as “Leptomeningeal (LM) effusion” or neoplastic arachnoiditis” [14,18,20]. The CSF pathway compromise is most likely if that occurs in posterior fossa [8]. In that instance 4<sup>th</sup> ventricle outlets outflow may be compro-

mised. The cisterna magna can become filled with neoplastic cells from the spread or extension of the tumor mass (usually in cervical segment [12,19]), disconnecting thecal sac from CSF flow. This may effect in communicating HC in the mechanism explained by the hydrodynamic theory [1,13]. By compromising cisterna magna and SAS of convexity with AGs included, the observed cHC results from impaired absorption of CSF in V-R spaces, AGs and perineural lymphatic vessels [3,5,7,12,16,17,19,20]. Rifkinson et al. also proposed obstruction of obex by tumor cyst as a cause of HC [19].

However, alluding to Alessia Imperato et al., 3 facts render this theory unlikely:

1. It usually appears only after tumor resection (10/12 cases analyzed in the article),
2. It does not always close the outlets of 4th ventricle,
3. HC was also observed when the cyst was not extending up to obex.

Thus, HC in this case is probably iatrogenic: due to postoperative adhesions impairing 4<sup>th</sup> ventricle outlets [36].

**Table 3:** Mechanisms of HC development: Tumor cells compromising CSF flow.

General mechanism	Specific mechanism	Type of HC	Supporting articles		Level of evidence
			Reference number	Amount	
Tumor dissemination	4 <sup>th</sup> ventricle outlets obstruction; Cisterna magna obstruction	oHC	4,18	2	3,5
	AGs compromise	cHC	6,18,19	3	3,5
LM Spread leading to SAS compromise	Neoplastic arachnoiditis; LM effusion	cHC	1,3,5,6,8,10– 12,15,18,19,21	12	2,3,5
Tumor extension	Obliteration of CM	oHC>cHC	4,18	2	3,5
	Obex obstruction	unlikely	1,10,18	3	3,5

### Hydrodynamic theory

According to this theory, the thecal sac, thanks to its velocity and elasticity, functions as a CSF reservoir providing about 30-70% compliance alongside the intracranial vascular pool [37]. If imbalance like temporary CSF overproduction or under-absorption occurs, the thecal sac SAS allows compensation for the difference in CSF velocity without major changes in ICP [37]. Those minor velocity fluctuations occur physiologically and are synchronized with cardiac rhythm; they become more prominent if a reservoir becomes smaller or more rigid - e.g. in the presence

of a spinal tumor. This obstruction in SAS “disconnecting” thecal sac from cranial SAS results in increased intracranial CSF pulse pressure, referred to as “the water hammer effect”. Those temporary fluctuations in CSF velocity not being buffered by spinal sac are proven to be sufficient to cause ventriculomegaly and aggravate the effects of other factors that cause HC [1, 13]. The CSF absorption also occurs around spinal nerve sheaths. The portion of CSF varies among patients; in some may be residual, in others significant. Thus, if impaired by tumor disconnecting a part of thecal sac, could cause cHC solely [1,8].

**Table 4:** Mechanisms of HC development: Hydrodynamic theory.

General mechanism	Specific mechanism	Type of HC	Paper		Level of evidence
			Reference	Number	
Hydrodynamic theory	Reduction in compliance due to thecal sac obstruction/ stiffening - <i>water hammer effect</i>	cHC	1,5	2	3,5
	Impaired CSF absorption around spinal nerve roots	cHC	11	1	2

### Substances compromising CSF flow – mainly absorption

As Harris et al. and Gardner et al. have documented, elevated CSF viscosity is often linked with risen ICP [1,12,19,22]. This phenomenon is due to an increased protein content – proteinorachia, also called eponymically as the Froin’s syndrome [38]. In further studies, it should be aimed to identify of all these proteins produced by tumors and possibly causing HC. The mere rise in fluid osmolality results in increased fluid production, possibly leading to the development of hydrocephalus [35]. One should be aware that elevated tumor cells in CSF does not correlate with metastases risk [19]. One of the proteins, that has been repeatedly found elevated in patients with proteinorachia is fibrinogen [1,3,5,8,22].

Few mechanisms can lead to its concentration rise. G. Cinalli, et al. propose that one of them is chronic inflammation (causing fibrinogen production as an acute phase protein); this has been documented in all (4) of described cases [8]. Borgensen et al. have described, that in case of intradural tumors the Blood-Brain Barrier (BBB) is compromised – the tumor’s vasculature is not histologically coherent with physiological vasculature, where BBB exists. That leads to leakage of fibrinogen into SAS [39]. A similar case can be the one proposed by Rifkinson et al., when tumor cyst communicates with SAS, releasing its contents, including fibrinogen, into the SAS [1,19]. Another well-established cause of

the fibrinogen elevation is SAH from the tumor [40]. The most comprehensive description of the sequence in which fibrinogen leads to irreversible impairment of CSF flow, resulting in HC, was published by Borkar et al., summarized in successive events as a list below:

1. Anormal CSF fibrinogen and its conversion to fibrin increases outflow resistance by compromising AGs [41].
2. CSF stagnates and subsequently forms fibrin nets in the cerebral convexities and cranial base SAS. Then it organizes into fibrous tissues [42].
3. Subarachnoid adhesions allow for further neoplastic cells implantation – in case of IDI, and leptomeningeal dissemination post-operatively (surgery,shunting) – in case of intracranial neoplasms [43].
4. The tumor spread described in point 3 creates a self-sustaining and permanent state.

It explains why HC infrequently resolves after tumor excision and often occurs even after that – leading to the high mortality [44]. The venous pressure can be elevated in the presence of a neoplastic disease [45,46]. The impaired CSF reabsorption due to increased venous pressure also contributes to or exacerbates HC, which has been proven by Dreha - Kulaczewski et al [35,46].

**Table 5:** Mechanisms of HC development: Substances compromising CSF flow.

General mechanism	Specific mechanism	Type of HC	Paper		Level of evidence
			Reference	Number	
CSF osmolality elevation regardless on the substance	Elevated protein (no substances specified)	oHC	1,3,4,8,10,11,13,19,21,47	10	2,3,5
	Froin’s syndrome (no substances specified)	cHC	3,5,6,17	4	5
Increased fibrinogen concentration	SAH	cHC/oHC	3,22,24	3	5
	CSF stagnation increases fibrin formation	cHC	1,21	2	3,5
	Fibrin eases mets implantation	cHC/oHC	21	1	5
	AGs compromise	cHC	6,18,19	3	3,5
Venous hypertension	Decreased CSF absorption at all sites	cHC	35,45,48,49 <i>*additional papers, not included in original research</i>	4	3,5

### Substances in CSF promoting lm cells proliferation

The release of a tumor-generated chemicals into the CSF can lead to elevated intracranial pressure in cases of coexisting pseudotumor cerebri or HC [47]. Various substances contained in CSF due to infection, trauma and neoplastic infiltration can induce leptomeningeal cells to proliferate, eventually causing fibrosis, SAS compromise and HC [48]. This effect was mentioned as “leptomeningeal effusion”. Motohashi et al. have found that thrombin, TGF- β, EGF, aFGF and PDGF promote LM cells proliferation, and TGF-β1 also enhances the proliferative effect of thrombin and EGF on LM cells [49]. Thus, these substances may be an additional, indirect cause of HC. Given the current findings on the regulation of CSF volume, it should also be considered, that the mere presence of these substances, if increasing its osmolality, will contribute to CSF overproduction [45,50].

### Discussion

**CSF circulation updated model** We have performed an additional review of the recent literature on CSF circulation and summed up what it proposes below.

#### Classical model

The classical model implies that CSF is mainly produced in choroid plexus of lateral, third and fourth ventricles. Than it flows through the fourth ventricle outlets to basal cisterns’ Subarachnoid Space (SAS). There, moving upwards around cerebral convexities’ SAS it is absorbed by Arachnoid Granulations (AGs) into Superior Sagittal Sinus (SSS), being returned into the blood. Some portion of CSF would descend into the thecal sac SAS and then enter basal cisterns SAS again to be eventually reabsorbed into SSS [51]. The dominant factor directing the above presented flow would be the pulsating Central Nervous System (CNS) vessels. In

recent years, the classical model of fluid circulation has been repeatedly disputed on reasoned premises [45,50].

### Production

Beginning with CSF production, the experimental data contradict the thesis that the only structure relevant in this process is the choroid plexus. After removing those structures in animal and human subjects, the level of abatement in fluid delivery is inconsistent with that which should occur if the Choroid Plexus (CP) was its main source [52].

As an important complementary source of CSF, the authors of new research suggest endothelium of brain capillaries (via the Virchow-Robin (V-R) spaces) [53], and ependymal lining of ventricles as an additional one [51]; it is assessed that 15% up to 30% of CSF is formed off the CP, so it does not necessarily enter the lumen of the ventricles originally [51].

### Flow and absorption

#### Unidirectional flow

Another concept of the previous paradigm, which is the unidirectional flow of CSF (from ventricles through SAS into AGs), also becomes doubtful in the light of Klarica et al. findings. After blocking the aqueduct of Sylvius in animal model, no ventriculomegaly was observed<sup>54</sup>; further experiments have shown that CSF can be absorbed all over the ventricular lining, and outside ventricles, into the V-R spaces and subsequently into cerebral microvessels [51,55].

#### Impetus

Furthermore, Dreha-Kulaczewski et al. have proven that it is not the pulsating brain vessels, but the breathing phase being the main force affecting CSF movement. During inspiration, when negative pressure increases venous return, more CSF is absorbed causing it to move from the spinal canal rostrally; and conversely during exhalation. The arterial pulse-related CSF flow was still observed, but this represented a very minor contribution. It must be noted, that the described research was carried out using the MRI technique, thus all subjects were in the supine position - the findings may deviate from the ones above if investigated in the

upright position [45, 46, 50]. This finding indicates that HC might be caused or catalyzed by elevated venous pressure, which would lead to impairment in CSF absorption [46].

### V-R spaces

The role of macroscopic AGs and microscopic Arachnoid Villi (AV) as the main CSF absorption site has also been marginalized and the attention has been shifted to the V-R spaces, cervical lymphatics and spaces around spinal nerve roots [35, 51]. It is implied that CSF remains in constant balance with brain interstitial fluid, all being produced and absorbed around capillaries, in V-R spaces – so it could be absorbed (and produced) everywhere - from all the ventricular system [55] and SAS [35, 51].

### Cervical lymphatics

Cervical lymphatics may play a significant role in CSF absorption. The fluid can reach there via the following 2 routes: along the subarachnoid space of exiting cranial nerves or, as previously pointed out, down the Virchow–Robin space of arteries and veins penetrating brain parenchyma [35].

### Venous plexuses

Dural venous plexuses has been reported to be an additional, minor sites of CSF absorption. The fact that AGs and AVs are not fully developed at birth, may indicate that some portion of CSF relies on the venous plexus of the inner surface of dura; mostly in infants [35].

### Spinal nerve sheaths

An additional route of CSF absorption is its uptake around the spinal nerve sheaths. Herein this mechanism gains particular importance if a neoplastic mass occluding SAS of the thecal sac at a relatively high level is present [8,56].

### CSF volume regulation

The fluid volume is dependent on the hydrostatic pressure and osmotic force within the CNS between the capillaries on one side and the interstitial fluid and CSF unit on the other. Venous pressure is also crucial for the absorption, and thus for the volume of fluid - as it rises, the rate of fluid uptake decreases [51]. The

**Table 6:** Comparison of classical and updated CSF circulation models.

CSF circulation phase	Classical model	Updated model		Supporting articles
		Findings	suggested mechanisms	Amount
<b>Production</b>	Choroid plexus	No significant decrease in CSF after CP resection	1. CP 2. CNS capillaries endothelium (V-R spaces) 3. Ventricular lining	9
<b>Flow</b>	Unidirectional: CP→AoS*→AGs	No ventriculomegaly after AoS blockage	1. CSF can be absorbed also over ventricular lining	4
<b>Absorption</b>	AGs,AVs→SSS	Diminished AGs & AVs involvement; multiple novel absorption sites	1. VR spaces 2. AGs, AVs 3. Cervical lymphatics (via V-R spaces/along cranial nerves) 4. Dural venous plexuses 5. Spinal nerve sheaths	11
<b>Impetus source</b>	Pulsating CNS vessels	Strong correlation between respiratory phase, venous pressure & CSF absorption	1. Breathing phase (inspiration promotes CSF upward motion and conversely) 2. Pulsating CNS vessels	3

choroid plexus still seems to be the most important in secretion, and as far as absorption is concerned, AGs would be an additional route beside the major pathway: through the epithelium of brain vessels in V-R spaces [35,51,55].

There are another two new hypotheses arise from novel theories of CSF dynamics. The first concerns venous hypertension. It has been observed that some neoplasms compromise systemic hemodynamics, and may effect in elevated venous pressure; [46] also iatrogenically [57]. Adding reduced compliance of thecal sac, which causes previously described water hammer effect, 1 those two factors may significantly contribute to HC development. The second theory would involve the fact, that CSF volume appears to be regulated by its osmolality [35,51]. Increased CSF viscosity that is frequently observed in the presence of spinal tumor, [1, 12,19,22] irrespectively of the specific substances, could alone aggravate CSF dynamics changes.

### Clinical conclusions

#### Shunting

The insertion of intraventricular shunt should be avoided before spinal tumor resection. First reason is that HC may subside after the tumor removal (especially in extramedullary tumors). Also, shunt can reverse the CSF flow, excluding intracranial SAS and CSF renewal, thus inducing it's collapse and promoting further adhesion and tumor cell implantation [36]. Another risk is causing upward spinal coning. This phenomenon occurs when collection of CSF above the level of spinal tumor causes pressure drop and subsequently pulls up the tumor, partially or totally strangulating spinal cord vessels and causing spinal cord compression symptoms [58]. In case of intramedullary lesions, HC is much less likely to subside after resection than in case of extramedullary tumors [43].

#### Neuroimaging

MRI with contrast enhancement should be performed to rule out intracranial leptomeningeal seeding as the cause of HC; if it's present, CSF shunt should be inserted during the same operation [36]. A neuroimaging follow-up should be performed to look for and potentially treat late-onset HC. According to Sung et al., it affects 23% of patients; 75% with IDI and 50% with Intradural Extramedullary (IDE) lesions. Late-onset HC in 62% of described population was induced by leptomeningeal seeding of the spinal tumor [36]. Patients with symptoms of HC or confirmed ventriculomegaly with no clear cause, who develop any spinal deficits, should be highly suspected for a spinal neoplasm and an MRI of the spine should be performed.

#### Lumbar or cisternal puncture

Despite the risk of upward spinal coning described above, studies have proven that in terms of puncture among patients with spinal tumors, cisternal instead of lumbar puncture is safer. Here the risk of downward spinal coning is more real: The reservoir below the tumor is much smaller than above it [59]. Thus, cisternal puncture will not influence CSF pressure as much as LP would, and it should be the choice among patients with spinal tumors [36].

### Limitations

Drawing conclusions regarding the occurrence of hydrocephalus in the general population, the type of tumor most frequently causing HC, on the basis of the information presented in the tables, is not likely to be reflected in reality. The analyzed populations are not representative for such considerations, and the quantifiable information presented in these tables is only demonstrative.

Similarly, the amount of studies mentioning a certain hypothesis or confirming it (summarized in the tables) is not a proof of greater validity of such a hypothesis - rather its popularity. None of the papers analyzed on the mechanisms through which ISTs result in HC has taken into account recent reports on CSF circulation. Hence, these mechanisms are based on the classical model of CSF circulation. We have analyzed them in the light of these reports, however, we carried out no experiments on real objects, so these deliberations are purely theoretical.

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