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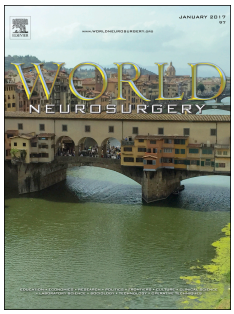

Choroid plexus in the central canal of the spinal cord causing recurrent syringomyelia

Anan Shtaya, MD, MRCS, PhD, Ahmed-Ramadan Sadek, DPhil(Oxon), FRCS (SN), James AR. Nicoll, FRCPath, Ali Nader-Sepahi, FRCS (SN)

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Choroid plexus in the central canal of the spinal cord causing recurrent syringomyelia

Anan Shtaya MD, MRCS, PhD [1, 2], Ahmed-Ramadan Sadek DPhil(Oxon), FRCS (SN)[2], James AR Nicoll FRCPath [3] & Ali Nader-Sepahi FRCS (SN)[2]

[1]Neurosciences Research Centre, Molecular and Clinical Sciences Research Institute, St George's, University of London, London, UK.

[2]Wessex Neurological Centre, University Hospital Southampton, Southampton, UK.

[3]Clinical Neurosciences, Clinical & Experimental Sciences, University of Southampton, Southampton, UK.

Corresponding Author:

Anan Shtaya

Neurosciences Research Centre, St George's University of London

London, SW17 0RE, UK

E-mail ashtaya@sgul.ac.uk.

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Conflict of interest

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Abstract:

Background: Syringomyelia is a fluid filled cavitation within the substance of the spinal cord. This condition usually follows a primary pathology that disrupts the normal CSF circulation or disturbs the microcirculation and cytoarchitecture of the spinal cord parenchyma. However, an aetiology of recurrent syringomyelia resulted from an ectopic choroid plexus (CP) has not been discussed. Ectopic CP rests may be found within the central nervous system. Although there has been a single report, describing ectopic intramedullary spinal cord CP, to our knowledge, extra-cranial non-malignant CP in the central canal of the spinal cord has not been reported.

Case description: We report CP in the central canal of the spinal cord in a 23-year-old male patient who had developmental delay and diabetes mellitus type I who presented with dissociated sensory changes and muscle wastage predominantly on the right upper and lower limbs. MRI demonstrated a multi-loculated spinal cord syringomyelia stretching from cervical (C3) to the conus medullaris causing recurrent neurological deficits. Central canal spinal cord lesion's biopsy revealed CP. Decompression and syringo-subarachnoid shunt insertion stabilised the patient’s neurology.

Conclusion: Our illustrative case reveals the presence of CP in the central canal of the spinal cord that may suggest a role in the aetiology of recurrent syringomyelia. While management poses a challenge to neurosurgeons, prompt decompression and shunting of the syringomyelia remains a favourable approach with acceptable outcomes. Further investigation into the pathophysiology of central canal CP ectopic causing recurrent syringomyelia and its correlation with spinal cord development may help future treatments.

Key Words: choroid plexus, spinal cord, syringomyelia, ectopic, development.

Introduction

Syringomyelia may be due to primary spinal injury, inflammation, or infection and mechanical causes disturbing normal CSF circulation[1]. Furthermore, any blockage or disruption of CSF passage from the fourth ventricle to the subarachnoid space following downward displacement of the cerebellar tonsils mostly in Chiari I malformation may contribute to the pathophysiology of syringomyelia[2]. However, syringomyelia due to ectopic CP has not been described. The CP is a villous and vascular structure with a neuro-ectodermal epithelial origin[3]. It develops from the dorsal roof of the ventricular system which is covered by the neuro-ectodermal epithelium originally consisting of ependymal cells[3]. Interestingly, the ependyma lining of the central canal of the spinal cord harbours potential neural stem cells that can be activated after spinal cord injuries[4]. Neural progenitor cells reside mainly within the sub-ventricular (sub-ependymal) zone of the lateral ventricles and the dentate gyrus of the hippocampus[5-7]. Newly born neurons migrate in chains of cells towards the anterior portion of the lateral ventricles and contribute to the formation of olfactory blub neurons through rostral migratory stream[5, 8, 9]. CP has a role in regulating neural precursor cell migration; indeed Clarke et al in 2006 demonstrated an increase in CP that resulted in a reduction in migration and function of the newly born neurons in the olfactory bulb, which may suggest an important developmental role. CP has been described in the sacral region[10], cerebello-pontine angle[11, 12] and in association with trigeminal neuralgia[13]. However, CP has not been described in the central canal of the spinal cord and thus any possible role not only in the aetiology of recurrent syringomyelia but also in spinal cord development has yet to be addressed. Furthermore, CP may mediate effects of peripheral inflammation in the nervous system by altering gene expression profile after an inflammatory stimulus[14]. On the other hand, systemic non-inflammatory disease may enhance an inflammatory reaction in CP as seen in an autopsy of the CP of two patients treated for diabetic ketoacidosis[15]. However, any correlation between ectopic CP causing recurrent

syringomyelia that forms cavitation and inflammatory changes have yet to be clarified. Herein, we report a complex case of recurrent syringomyelia in a patient with developmental issues and type 1 diabetes mellitus who was found to have ectopic CP in the central canal of the spinal cord. The clinical presentation, imaging, pathology and management are discussed.

Case Report

This 23-year-old left-handed man was born at 27 weeks of gestation. Developmentally he presented with manifested motor delays and walked when he was two years old. Cognitively he had no developmental delays. He developed insulin-dependent diabetes mellitus. Subsequently he was diagnosed with Scheuermann's kyphosis with a gentle scoliosis that was managed conservatively in a brace. He had a two-year history of reduced pain and temperature sensation in the right forearm and hand. On examination, he had café au lait spots but no axillary freckling. There was right hemi-facial atrophy. His right hand and foot were smaller than the left side. There was dissociated sensory loss on the right side of his upper and lower limbs. His power was normal at this stage.

MRI scan demonstrated a multi-loculated spinal cord syringomyelia cavities stretching from C3 to the conus medullaris. There was no hindbrain herniation. A syringo-subarachnoid shunt was inserted at T1-2 level in order to halt the progression of the spinal deformity and neurological deterioration.

A small biopsy of the spinal cord did not reveal any abnormality. Neurologically he remained stable. A postoperative MRI scan showed satisfactory resolution of the syringomyelia. Three years later, shortly after a fall, he developed a T4 sensory level and spastic paraparesis and became wheelchair bound. An MRI scan demonstrated re-expansion of the syringomyelia cavities below the previously operated level (Figure 1). The thoracic laminectomy was extended in the standard surgical approach and another syringo-subarachnoid shunt was inserted. Once the midline myelotomy was made, we noted, under the operating microscope,

delicate pink frond-like tissue resembling choroid plexus in the central canal of the spinal cord (the syringomyelia cavity) (Figure 2). Biopsies were obtained and this tissue was coagulated. Intraoperative smear preparations confirmed the tissue to be choroid plexus. Subsequent paraffin histology showed this to be heterotopic choroid plexus with no features of neoplasia (Figure 3). He remained stable and went on to make a good recovery with spinal rehabilitation without evidence of recurrence eight years down the line.

Discussion

The whole of the central nervous system (CNS) is derived from ectoderm apart from its blood vessels and some neuroglial elements. However, it has been demonstrated that all regions of the neural ectoderm which subsequently form the brain have the potential to form a choroid plexus lineage in an *in-vitro* mouse model [16]. Ectopic choroid plexus rests can be found in the CNS. It has been described within the spinal cord [17], in the pre-sacral region [10], in the cerebellopontine angle [11, 12] and even associated with a case of trigeminal neuralgia [13]. Although ectopic CP was reported in an enhanced lesion within the spinal cord[17], we describe the first case of ectopic choroid plexus within the central canal of the spinal cord as part of a complex syringomyelia in a patient who had developmental delay, type I DM and a history of trauma who presented with neurological deficits due to recurrent syringomyelia. We know strictly speaking that a fluid filled cavity surrounded by the ependymal cells of the central canal is hydromyelia[18]. Hydrosyringomyelia is another term that can be used in our case. The syringomyelia may has started as hydromyelia and progressed to hydrosyringomyelia as it extended into the cord parenchyma as it expanded beyond the central canal. However, we have employed the terms syrinx and syringomyelia as the radiological diagnosis in this case has been a spontaneous/idiopathic syringomyelia, and there was no evidence of ependymal cells.

Developmentally, even before the neural tube has completely closed it is divided into a large cranial part that forms the brain, and a caudal tubular part, which forms the spinal cord. The cavity of the caudal cylindrical part of the neural tube is called the dorsoventral cleft. The lateral walls of the cavity are thick but the roof (dorsally) and floor (ventrally) are thin. The walls of the tube differentiate into the matrix cell layer, the mantle layer and the marginal layer. Cells from the matrix cell layer differentiate into ependymal cells. The ependymal cells of the central canal show several structural differences from those of the ventricles[19]. These cells display a high proliferative capacity and are able to differentiate into multiple cell lineages as evidenced from a spinal cord injury research model[20, 21]. Congenital or perhaps perinatal injurious stimuli and inflammatory changes may be the precedent for a developmental cascade leading to the formation of choroid plexus within the central canal. Choroid plexus formation and differentiation is induced by extracellular factors such as growth factors, and extracellular matrix components produced by mesenchymal cells [16] or cell-matrix interactions without direct participation of the mesenchyme [16]. CP secretes growth factors such as epidermal growth factor, basic fibroblast growth factors, vascular endothelial growth factor, transforming growth factors, insulin-like growth factors and bone morphogenetic factors. It has been demonstrated that these different growth factors also enhance proliferation of neural stem cells and neurogenesis[22]. Furthermore, Nielson and Dymecki [23] demonstrated that sonic hedgehog (Shh) protein produced by hindbrain choroid plexus epithelium acts on the progenitor pool for CP epithelial cells and on CP pericytes to induce extensive vascular outgrowths. In this regard, it has been shown that Shh has a role in neural stem cell activation in mice model of traumatic brain injury[24]. Although we have not measured growth factors or Shh in the CSF of our patient, the preceding facts may suggest that the secretion of growth factors from ectopic CP enhances the generation of new CP and vice versa, it is possible to speculate that Shh may have a role that contributes to the

expansion of the syringomyelia. Measuring these proteins in the CSF of these patients and further investigations into this mechanism might be useful to understand the pathophysiology. Our patient was born at 27 weeks gestation and required a prolonged course of mechanical ventilation in intensive care. He sustained developmental delay and neurological deficits. He developed complex syringomyelia cavitation and found to have CP ectopic within the central canal of the spinal cord. He was also diagnosed with type I DM. His MRI revealed a thin spinal cord. The abnormal presence of CP in rodents' studies reduced neuroblasts migration to the olfactory bulb and affected their development and function[8]. This theory may help in understanding our complex case. In this regard, the abnormal presence of CP may not only contribute to syringomyelia expansion but also hinders neurogenesis (the generation of new neurons) and perhaps had some effects on the spinal cord development therefore, we observed, in our case, a thin spinal cord with longstanding discrepancy between limbs (right side is smaller than left). It is also possible that interplay of growth and transcription factors washed down from hindbrain CP and carried in the CSF, lays at the root of this anomaly leading to the seeding of CP rests within the central canal and contributes to the pathology. Further investigations into those possible mechanisms may help understanding this complex case and possible future ones and contribute to their treatment.

We believe that this patient's extensive multi-loculated syringomyelia was secondary to the presence of ectopic rests of CP within the central canal of the spinal cord. This might be a result of developmental/inflammatory changes, which affected the spinal cord genesis and influenced the generation of more CP. There was no evidence of an intracranial choroid plexus papilloma or drop metastases. The recurrence of symptomatic syringomyelia may be due to shunt blockage and enlargement of the cysts after the trauma. We know that trauma enhances cell proliferation, as such proliferation and growth of CP may be another theory supporting the increase in CSF production and hence syringomyelia. The CP in Figure 2 was

biopsied and coagulated. However, there may be other functional ectopic CP throughout his central canal or syringomyelia cavities, which continues to produce CSF. Although we anticipate that this patient will continue to pose a challenge in management to us and perhaps more neurological problems, he is doing well eight years after his last operation with no new neurological changes. This may be due to a functioning shunt or perhaps optimistically our coagulation of the main CP that was biopsied during his last surgery contributed to his stabilisation, but we are unsure about the latter. Overall, early and prompt neurosurgical intervention with close follow-ups and serial MRI studies might stabilise the patient condition as in our situation.

In conclusion, CP within the central canal of the spinal cord as a possible cause of recurrent symptomatic syringomyelia has not been reported. The presence of CP in such location may have developmental and/or inflammatory mechanisms and yet to be explored. Understanding the pathophysiology of ectopic CP and its correlation with syringomyelia may be a good research venue to target future therapy for these cases. The management of these patients remain a challenge to the neurosurgical community.

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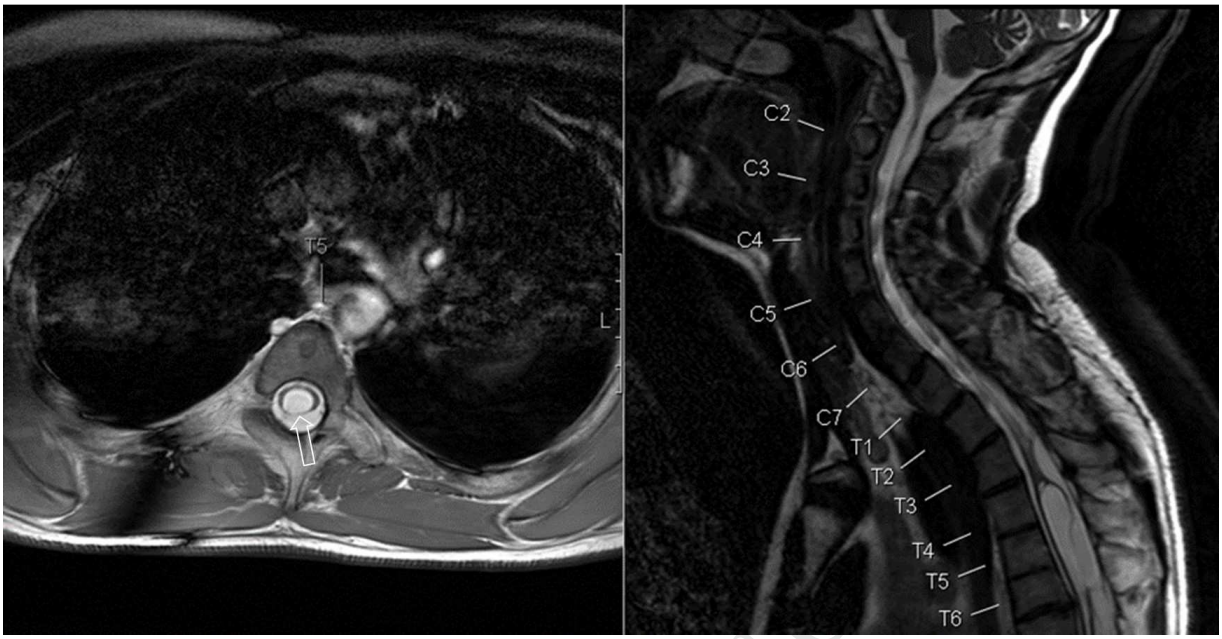
Figure legends

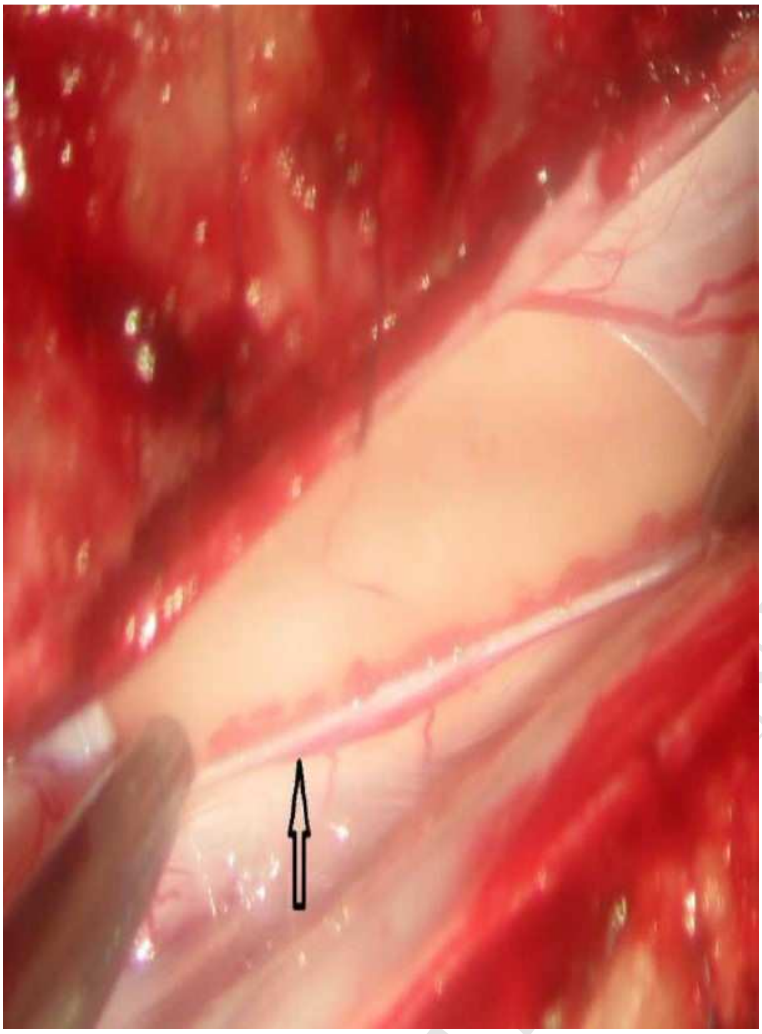
Figure 1. MRI images before the last surgery. A T2W sagittal image demonstrating the syringomyelia extending from C3 vertebra down as well as thin spinal cord. B. An axial T2W

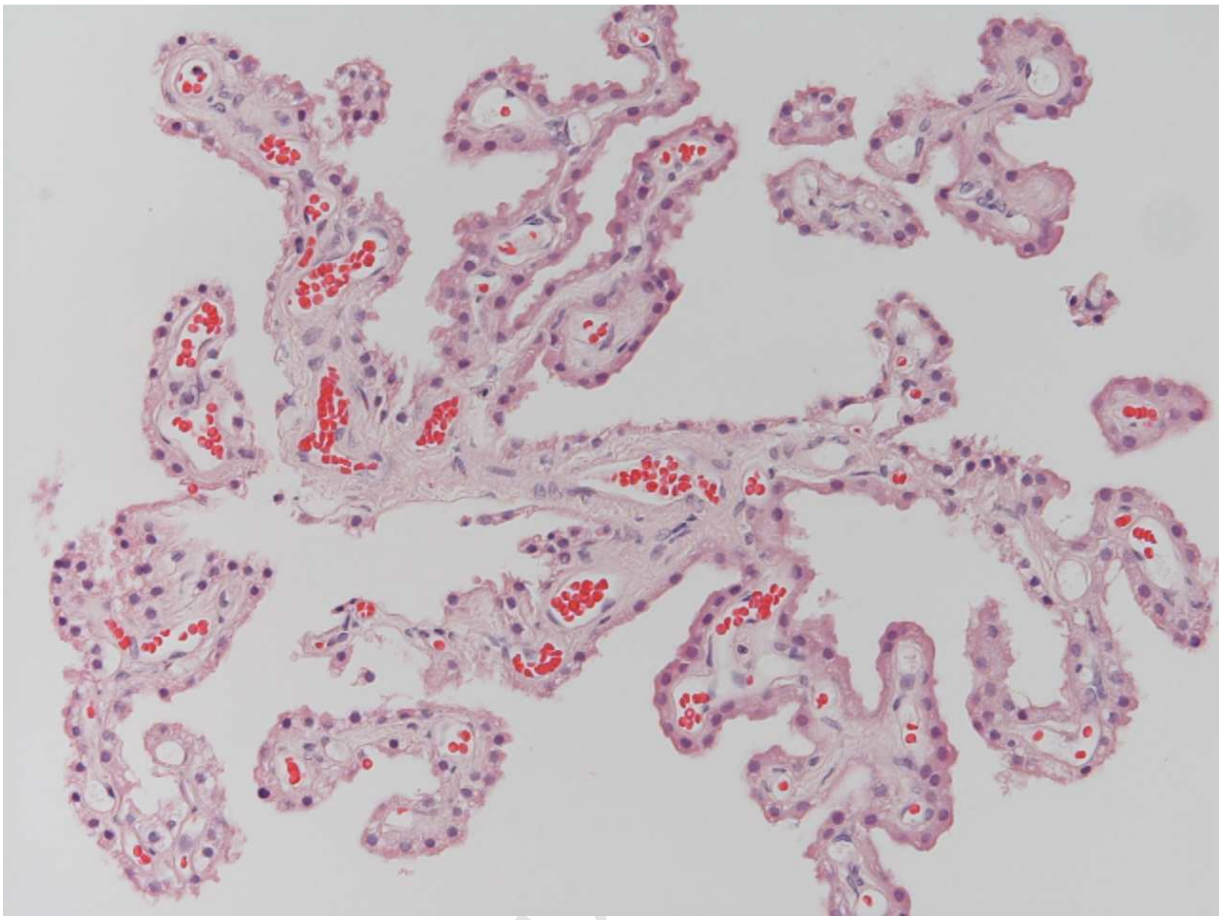
image at T5 level showing the CSF syringomyelia cavity in the central canal of spinal cord (arrow).

Figure 2. Intraoperative picture demonstrating a delicate pink frond-like tissue resembling choroid plexus within the syringomyelia in the centre of the spinal cord canal (arrow).

Figure 3 Paraffin histology showed tiny fragments of choroid plexus tissue. The appearances are those of papillary structures formed of fibrovascular cores surrounded by a single layer of cuboidal epithelium with a cobblestoned surface (haematoxylin & eosin x20).







Highlights:

Manuscript title: Choroid plexus in the central canal of the spinal cord causing recurrent syringomyelia

- Ectopic choroid plexus (CP) in the central canal of the spinal cord.
- Ectopic CP causing recurrent syringomyelia with neurological deficits.
- The aetiology of this ectopic CP and its correlation with the patient's development is complex and warrant further research consideration.
- Treatment of recurrent complex syringomyelia remains a challenge to neurosurgical community.

Abbreviation:

CP: Choroid plexus:

MRI: Magnetic resonance imaging.

T2W: T2 weighted.

T: Thoracic.

C: Cervical.

CNS: Central nervous system.

CSF: Cerebrospinal fluid.

DM: diabetes mellitus.

Shh: sonic hedgehog