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Research paper

The early history of Pallister–Hall syndrome—Buried treasure of a sort

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ABSTRACT

Pallister–Hall syndrome was initially recognized under fairly unique circumstances involving exhumation of the very first case. The first two cases had dramatic and unusual features including a hypothalamic hamartoblastoma, imperforate anus, an unusual type of polydactyly with the extra digit being central, hypopituitarism with secondary hypoadrenalism, and lethality after birth (probably due to hypoadrenalism). Within a short time frame, four additional cases were identified. As the full spectrum and variability of anomalies was recognized, it became clear that it was not such a rare disorder. Shortly after familial cases were recognized, the responsible gene was identified at *GLI3*. However, since other different conditions also involved *GLI3*, elaborating the domains of the gene and the types of mutations needed to be defined in order to have a clear correlation of the genotype–phenotype relations.

The stories about how clinical syndromes are recognized are always interesting—medical detective stories. They reflect the curiosity that is part of human nature, and the knowledge and diagnostic capabilities of the time. Pallister–Hall syndrome (PHS) is no exception. Its history also reflects the importance of unique (sentinel) features during the early recognition stage of a clinical syndrome and the remarkable lengths to which "the curious" will sometimes go in order to describe and define a case.

In the early 70's, it was the tradition for the Shodair Hospital in Montana to have conferences each summer related to new developments in the medical field for the health care providers in western Montana. Phil Pallister (a family physician who had intentionally gone to a very rural area after World War II), was interested in intellectual disability and genetics, and was the organizer of these conferences. Dr. Pallister's family welcomed the visiting faculty and always showed them the special features of "Big Sky" country, including trips into the hills looking for Indian artifacts, whole pig roast banquets, and local hospitality with "tall tales" about their previous escapades. Pallister brought experts from all over the world in order to learn from them and they in turn learned about the goodness and humanity of this "country doctor". It was a special privilege to be invited. Almost always there were "unknowns" (unusual patients for whom a diagnosis had not yet been made) presented for possible diagnosis by the visiting experts.

The summer of 1978, Dr. Pallister presented to the conference the history of a child with a not particularly surprising set of congenital anomalies (polydactyly and imperforate anus) (Table 1). However, the question raised was somewhat unique. Should the baby, having been buried, be exhumed to try and make a specific diagnosis? The family were anxious to have another child and the affected baby who had been born and died six months earlier, had been buried without embalming or an autopsy. The information from the available X-rays suggested that a specific diagnosis would not be achieved by exhumation particularly from an unpreserved body. The X-rays did not show the pathognomonic features of the possible lethal conditions with polydactyly which had been described by the late 1970s.

It is worth noting that soft tissue imaging and DNA studies were not even a "twinkle in the diagnostician's eye" at that time. The attendees, the experts, and other individuals who had been consulted on the case, thought Dr. Pallister had done a reasonable job on the basis of available information of trying to make a diagnosis; and therefore, they recommended that exhumation would not yield any new useful information. They went a bit further to say that since a specific diagnosis could not be made, the recurrence risk was probably quite small. Dr. Pallister, who had been asked to provide genetic counseling to the family, conveyed this information to the family and the referring physicians.

Shortly after returning home to the "big city" of Seattle, I was called for a consultation on a baby who had been transferred from a small town in Western Washington to Seattle Children's Hospital (Children's Orthopedic Hospital at that time) for surgery. This baby also had imperforate anus and polydactyly. The question for me as the genetic

Abbreviations: PHS, Pallister–Hall syndrome.

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Table 1
Pallister–Hall Syndrome Timeline.

February 27, 1978	Child born by C-section in southwest Montana with congenital anomalies (polydactyly, malformed legs, and anal atresia). It lived 9 h and was not fed.
February 28, 1978	X-rays done, no autopsy. The child was buried.
March 27, 1978	Pallister was consulted and reviewed the X-rays. Shallow pituitary fossa, unusual 4th metacarpal, and abnormal air distribution in the abdomen; this led to questioning possible diagnosis of Ellis–van Crevald +/− tracheosophagal fistula.
April 17, 1978	Consultation with Jürgen Spranger—the child did not represent any of the known short rib/polydactyly chondrodysplasias
July 5, 1978	Shodair Annual Genetics Seminar the case was presented for discussion. All agreed it was an unknown since the pelvis was atypical for known polydactyly chondryodysplasias. Exhumation would not help since the child did not fit the known disorders.
July 4, 1978	Second child with polydactyly and imperforate anus born in Western Washington transferred to Seattle and stabilized. Genetic consultation concerning undertaking surgery. Recommended that since it was a "unknown" disorder, surgery should go ahead
July 5, 1978	During surgery for a decompression sigmoid colonoscopy, the child suffered a hypotension episode, never regained consciousness and became respirator dependent.
July 11, 1978	The second child died with severe coagulopathy, seizures, and renal shutdown.
July 12, 1978	Autopsy revealed complete absence of pituitary, bilateral adrenal hypoplasia, hypothalamic hamartoblastoma, cleft larynx, small kidneys and liver, in addition to the polydactyly and imperforate anus.
July 24, 1978	First case exhumed.
July 26, 1978	Taken to Seattle by Phil Pallister, and then autopsied by Bruce Beckwith.
1978–1979	Presentations of cases at various meetings yielded 4 more lethal cases with hypothalamic hamartoblastomas. A common theme among the cases was exposure to insecticides and/or herbicides. Multisystem structural and growth abnormalities tabulated together with differential diagnosis and published by Clarren et al., 1980 and Hall et al., 1980.
1982–1985	Many additional single cases published, considered extremely rare.
1986–1996	Familial cases with a wide range of variability began to emerge. Significant variability within a family. Maybe it was not so rare.
1996	NIH workshop of interested parties on PHSx to define appropriate workup and minimal features, and called for gene mapping, characterization of natural history, and development of resources for families, clinicians and researchers.
1997	GLI3 identified as responsible gene.
1997–2000	Functions of GLI3 mutations worked out (e.g., the role of various domains).

consultant, was whether or not the baby should be operated upon to provide diversional colostomy in view of the many additional anomalies—or was it a hopeless situation? The combination of polydactyly and imperforate anus quickened my pulse remembering the infant from Montana who had died unexpectedly shortly after birth. Could this new baby have the same thing? What did two similarly affected babies being born so close together mean? Having thought about this kind of issue together with a number of other physician and geneticists just a week before helped me to sort out my advice and it was to go ahead and operate, since we didn't have a specific diagnosis and the prognosis should be good. The surgery would give the baby the opportunity to survive and we might be able to learn more about the condition. It is important to put into perspective that ultrasound, CAT scans, and MRIs were not available to define soft tissue at that time so, clinical experience weighed heavily.

It seemed to me that the infant would have an excellent chance of recovery once the imperforate anus had been repaired. Thus, the baby was stabilized and taken to the operating room. As has been well described previously (Clarren et al. 1980; Hall et al. 1980), the baby had a hypotensive episode during surgery; however, the decompressive sigmoid colonostomy was performed. Post surgery, he never regained consciousness, became respirator dependent, and oligouric. In spite of aggressive treatment, he deteriorated and developed severe coagulopathy, seizures and died. Such things happened then, not infrequently, and it was felt that the best effort to give the infant a chance had been made. Permission for an autopsy was given by the parents.

Enter another interesting character, Bruce Beckwith, who was the Chief Pediatric Pathologist at Children's Hospital at that time. Bruce, as a pathologist, was already a well known sleuth. During the post mortem, as he enumerated and photographed with great care, the multiple minor anomalies and the truly remarkable complex findings (Fig. 1). Over the course of the autopsy, he became more and more agitated and excited. When he opened the cranium and found the walnut sized tumor at the base of the skull (Fig. 2), he called lots of people down to the autopsy room to see something he had never really observed before. Bruce was a fairly formal and stayed individual until he got excited and this really excited him. The presence of the tumor was associated with a hypoplastic pituitary and subsequent hypoadrenalism (the probable cause of the hypotensive episode that eventually lead to death). Then he called upon the best neuroanatomists of the time to determine what the intracranial mass was—a hypothalamic hamartoblastoma!

It didn't take long for me to get to the phone. Back in those days, we were still going through operators for long distance calls, but I did get a hold of Dr. Pallister. I somewhat breathlessly told him about the really remarkable features in this second baby. AND that it might actually be worthwhile to exhume the Montana infant. The X-ray of that baby's skull had been somewhat unusual and the remaining bone might show an indentation and maybe there would be some tissue still remaining that would allow confirmation of a brain structural anomaly. What was going on? This was an era when teratogens were just beginning to be described—thalidomide, warfarin—was this possibly a new environmental teratogen to produce two such unusual cases presenting within months of each other?

Phil Pallister talked with the family, the coroner, and the sheriff in Montana to arrange for the baby to be exhumed. Phil trundled the baby into the back of his station wagon and drove straight through from Helena to Seattle, crossing two state lines (probably a little outside the law at the time). He stopped in George, Washington (there is actually a small town in eastern Washington called George) to call and say, "I am on my way. I've stopped for gas in George and will be there shortly". When I went to tell Bruce Beckwith that Phil was on his way with the exhumed baby, Bruce put his nose in the air, pinched it with his fingers and said, "This is really going to be a stinker"—high drama as the stage was set.

The death and burial had been five months earlier during the winter in cold Montana. Miraculously, since the baby had not eaten prior to its death, there were no anaerobic bacteria to break down the tissue, and the cold Montana winter had actually preserved the tissues surprisingly well (Fig. 1A).

So it was that late one afternoon in July 1978, we gathered in the pathology theater as Dr. Beckwith carefully examined the child from Montana. A pattern of abnormalities began to emerge as we stood there marveling: the same unusual type of polydactyly (Fig. 3), extra frenula, a very large tumor at the base of the brain (Fig. 2), pituitary hypoplasia, and many other minor anomalies were all present. All of us were excited, but also worried about seeing two individuals with such unusual anomalies born in the space of a few months. We were concerned that a new environmental agent was at work.

All of us talked about these two cases because of their striking and unusual features at the next several meetings we attended. Other cases began to emerge. By Christmas, three additional cases (from Florida, Alaska, and Quebec) had been identified. All had died in the newborn period. Another affected baby was born in the spring in Kansas.